ENDOCRINOLOGY

The BULLETIN of the ASSOCIATION for the STUDY of INTERNAL SECRETIONS

Volume Five

Published by the Association
1921

TABLE OF CONTENTS

ADENOMA OF THE THYROID WITH HYPERTHYROIDISM (THYROTOXIC ADENOMA). HISTORY OF THE RECOGNITION OF THIS DISEASE AS A CLINICAL ENTITY. A STUDY OF THE SYMPTOMATOLOGY WITH BASAL METABOLIC RATES. Walter M. Boothby, Rochester, Minnesota 1

A CASE OF DYSTROPHIA ADIPOSOGENITALIS. Franklin G. Ebaugh and R. G. Hoskins, Baltimore 21

DETERMINATION OF RELATIVE ACTIVITY OF THE THYROID LOBES. N. Worth Brown, Toledo 29

THE HYPOPHYSIS CEREBRI OF THE WOODCHUCK (MARMOTA MONAX) WITH SPECIAL REFERENCE TO HIBERNATION AND INANITION. A. T. Rasmussen, Minneapolis 32

THE CONTROLLING FACTORS IN AMPHIBIAN METAMORPHOSIS: A REVIEW. John F. Fulton, Jr., Cambridge, Mass. 67

BOOK REVIEWS 85

ABSTRACT DEPARTMENT 89

DIABETES INSIPIDUS AS A HYPOPITUITARY SYNDROME. G. Marañón, Madrid 159

HYPOPHYSIS TUMOURS IN DOMESTIC ANIMALS. H. A. Vermeulen, Utrecht 174

PHYSIOLOGICAL HYPERTHYROIDISM. Harlow Brooks, New York .. 177

DEGENERATIVE CHANGES IN THE SEMINAL EPITHELIUM AND ASSOCIATED HYPERPLASIA OF THE INTERSTITIAL TISSUE IN THE MAMMALIAN TESTIS. Albert Kuntz, St. Louis 190

THE SPECIAL SERVICE RENDERED TO THE HUMAN ORGANISM BY THE SYMPATHETIC AND PARASYMPATHETIC SYSTEM, INCLUDING BOTH NERVES AND GLANDS OF INTERNAL SECRETION. F. M. Pottenger, Monrovia, California 205

CHANGES IN THE ENDOCRINE GLANDS OF A TUMOR-BEARING FEMALE RAT. Frederick S. Hammett, Philadelphia 216

FURTHER OBSERVATIONS OF THE PIGMENT CHANGES FOLLOWING REMOVAL OF THE EPITHELIAL HYPOPHYSIS AND THE PINEAL GLAND OF THE FROG TADPOLE. Wayne J. Atwell, Buffalo ... 221

BOOK REVIEWS 233

ABSTRACT DEPARTMENT 239

ADRENAL INSUFFICIENCY. G. N. Stewart, Cleveland 283

THE MICROSCOPIC APPEARANCE OF TWO TESTES NINE MONTHS FOLLOWING UNILATERAL VASECTOMY. Homer Wheelon, St. Louis 307

THE INTERNAL SECRETION OF SANDSTROEM'S GLANDS. PARATHYROID HYPOFUNCTION AND ECLAMPSIA. Aldo C. Massaglia, Chicago 309

HYPOPITUITARISM — FROEHLICH TYPE. IN AN INFANT NINE MONTHS OLD. M. Boyd Kay, Detroit 325

EDITORIAL:

THE ADRENALS AND THE EMOTIONS 328

THE ACTION OF HYPOPHYSEAL EXTRACTS 329

BOOK REVIEWS 332
ABSTRACT DEPARTMENT 335
THE PARATHYROID GLANDS. A REVIEW OF THE LITERATURE. Walter M. Boothby, Rochester, Minn..... 403
EPILEPSY SUGGESTIVE OF ENDOCRINE RELATIONSHIP. Henry J. Van den Berg, Grand Rapids, Mich..... 441
DOES THE ADMINISTRATION OF THE ANTERIOR LOBE OF THE HYPOPHYSIS TO THE TADPOLE PRODUCE AN EFFECT SIMILAR TO THAT OBTAINED FROM THYROID FEEDING? Philip E. Smith and Garnet Cheney, Berkeley..... 448
THE INTERNAL SECRETION OF THE SPLEEN. Nathan B. Eddy, Edmonton, Canada 461
EDITORIAL:
ENDEMIC GOITER: ITS PREVENTION AND TREATMENT..... 476
BOOK REVIEWS 478
ABSTRACT DEPARTMENT 479
THE SIGNIFICANCE OF THE INTERNAL SECRETIONS IN DISTURBANCES OF METABOLISM AND DIGESTION. Prof. Dr. Arthur Biedl, Prag 523
ENDOCRINE PROBLEMS IN PELVIC SURGERY WITH SPECIAL REFERENCE TO VICARIOUS MENSTRUATION. Curtice Rosser, Dallas.. 537
THE NEW VIEWS AS TO THE MORPHOLOGY OF THE THYMUS GLAND AND THEIR BEARING ON THE PROBLEMS OF THE FUNCTION OF THE THYMUS. J. Aug. Hammar, Upsala, Sweden..... 543
A CLINICAL STUDY OF UNUSUAL DISTURBANCES OF THE ENDOCRINE GLANDS. Oliver T. Osborne, New Haven..... 574
REPORT OF A CASE OF HYPOPHYSEAL TUMOR, WITH RADIOGRAPH. Mary Lawson Neff, Phoenix, Ariz..... 577
THE HEART IN THE EXPERIMENTAL HYPERTHYROIDISM WITH SPECIAL REFERENCE TO ITS HISTOLOGY. Hirotoshi Hashimoto, Tokyo 579
CHANGES IN THE BLOOD PRESSURE IN A CASE OF HYPERVAGOTONIA CAUSED BY THE INTRAVENOUS INJECTION OF ADRENALIN. J. J. Izquierdo, Mexico City..... 607
EDITORIAL:
WHAT IS ENDOCRINOLOGY?..... 610
BOOK REVIEWS 613
ABSTRACT DEPARTMENT 617
CLINICAL REPORT OF A CASE OF GRAVES' DISEASE WITH RAPID IMPROVEMENT FOLLOWING THE ORAL ADMINISTRATION OF FRESH OX SUPRARENAL GLAND. S. Shapiro and David Marine, New York 699
TESTICULAR SUBSTANCE IMPLANTATION. L. L. Stanley, San Quentin, Calif. 708
THE IMPORTANCE OF VISUALIZING ESTABLISHED SCIENTIFIC DATA WITH REFERENCE TO THE SIZE OF THE BODY CELLS AND THEIR CHEMICAL SUPPLIES IN THE CIRCULATING BLOOD. Georgine Luden, Rochester, Minn..... 715
SOME NOVEL EFFECTS PRODUCED BY STIMULATING THE NERVES OF THE LIVER. W. B. Cannon, J. E. Uridil and F. R. Griffith, Boston 729
THE NEW VIEWS AS TO THE MORPHOLOGY OF THE THYMUS GLAND AND THEIR BEARING ON THE PROBLEM OF THE FUNCTION OF THE THYMUS. (Concluded.) J. Aug. Hammar, Upsala, Sweden 731

394536

EXPERIMENTAL DIABETES INSIPIDUS AND GENITAL ATROPHY. Percival Bailey and Fritz Bremer, Boston 761
EXTIRPATION AND TRANSPLANTATION OF THE THYMI IN LARVAE OF RANA SYLVATICA. Margaret Morris Hoskins, Richmond. 763
ENDOCRINE THERAPY IN CASES OF LOW BLOOD PRESSURE. George H. Hoxie, Kansas City 773
BOOK REVIEWS 777
ABSTRACT DEPARTMENT 779
INDEX FOR VOLUME V

MAR 2 1921

Volume V January, 1921 *Number 1*

Endocrinology

The Bulletin *of the* Association *for the* Study *of* Internal Secretions

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Endocrinology

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January, 1921

ADENOMA OF THE THYROID WITH HYPERTHYROIDISM (THYROTOXIC ADENOMA). HISTORY OF THE RECOGNITION OF THIS DISEASE AS A CLINICAL ENTITY. A STUDY OF THE SYMPTOMATOLOGY WITH BASAL METABOLIC RATES.*

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Recent advances in the practical application of indirect calorimetry have rendered it possible for the physician to measure accurately and fairly readily under standard conditions one of the most fundamental phenomena of life, namely, the rate at which the life process of combustion is proceeding within the body. Calorimetry, like the taking of the temperature, is a measurement of certain heat phenomena. Just as the thermometer has furnished the means of distinguishing accurately and readily two great classes of diseases, the febrile and the afebrile, indirect calorimetry similarly allows precise differentiation of three large groups of diseases: (1) diseases characterized by a normal rate of metabolism; (2) diseases characterized by an increased rate of metabolism, and (3) diseases characterized by a decreased rate of metabolism. Furthermore, just as there are various diseases with abnormal temperatures, there are several diseases that have per se abnormal basal metabolic rates. So far the most clearly

*Presented before the Harvard Medical Society, Boston, February 17, 1920.

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defined groups of cases with abnormal basal metabolic rates are those due to disturbances in the functional activity of the thyroid gland. In this paper I shall discuss the condition of hyperthyroidism due to adenoma of the thyroid gland which is entirely distinct from the hyperthyroidism of exophthalmic goiter.

The confusion in recognition and classification of diseases with hyperthyroldism, usually considered under the group name of exophthalmic goiter, (Parry's, Graves', or Basedow's disease), is due to the fact that there are at least two separate and distinct clinical entities, as yet generally unrecognized, classified under this one term: the one, true exophthalmic goiter and the other, adenoma of the thyroid with hyperthyroidism. For this reason, the pathologist has been unable to find a consistent histologic picture in all the cases diagnosed exophthalmic goiter by the clinician.

HISTORY OF THE RECOGNITION OF ADENOMA OF THE THYROID WITH HYPERTHYROIDISM AS A CLINICAL ENTITY

Möbius in 1887 suggested that Basedow's disease is due to an abnormally increased activity of the thyroid gland. Greenfield (1893) was the first to demonstrate a specific pathologic alteration in the thyroid gland as the cause of exophthalmic goiter; he showed that in exophthalmic goiter there is a characteristic increase in the parenchyma with simultaneous enlargement of the individual cells from a cuboidal to a columnar shape and a decrease in the size of the acini and a reduction in the colloid content. His studies were limited to six typical cases of exophthalmic goiter. Other observers found that frequently hypertrophy was present in insignificant amounts only or was entirely absent in some of the cases clinically diagnosed exophthalmic goiter. MacCallum (1905) and Kocher (1912) considered, however, that very small areas of hypertrophy, sometimes only a few cells in scattered acini, fulfill the requirements for the pathologic confirmation of the clinical diagnosis of exophthalmic goiter. The absence of hypertrophy in cases clinically diagnosed exophthalmic goiter was explained by the fact that the case was either atypical or of short duration. Lewis (1906) stated, however, that the secondary exophthalmic goiter of some years' standing does not differ histologically from the simple colloid or parenchymatous goiter unassociated with Basedow's syn-

drome. Wilson, in his report of 1908, recorded an apparent disagreement between the pathologic findings and the clinical diagnosis as then made in 20 per cent of the cases.

Clinically it was early recognized that under the generic name of Basedow's disease were atypical cases which were subdivided by various authors into more or less ill defined, inconsistent groups and designated as primary and secondary (Gauthier and Buschan), *formes frustes,* or *incomplete* (Marie), goiter heart (Kraus, Gitterman and Stern), sympathicotonic and vagotonic (Eppinger and Hess), Basedowoid (Stern), Basedowized (Kocher). Of these the syndrome described by Gitterman most closely resembles that designated here as adenoma of the thyroid with hyperthyroidism. Although Gitterman recognized the characteristic age of occurrence in these cases and the association of a goiter of long duration, he considered the syndrome essentially from the viewpoint of cardiac therapy.

Plummer has come to the conclusion from an intensive study of the clinical findings in the large number of cases of different types of goiter examined at the Mayo Clinic, that there are two separate and distinct clinical types of hyperthyroidism, each associated with a distinctive pathologic change in the thyroid gland; that in one type the hyperthyroidism associated with the clinical syndrome of true exophthalmic goiter is always accompanied by hypertrophy and hyperplasia of the thyroid gland: and that in the other type the hyperthyroidism, pathologically not associated with this typical hypertrophy and hyperplasia, but with the occurrence of adenoma in the gland, is due to the adenoma and that the resulting clinical syndrome is distinguishable from that occurring in true exophthalmic goiter. These conclusions were reported by Plummer in 1911 before the American Medical Association, but they first appeared in literature in his discussion of Marine's paper in 1912, as follows:

"Dr. Marine has done excellent work on the thyroid. My observations, however, do not confirm his conclusions that the anatomic changes in the thyroid in cases of exophthalmic goitre are neither constant nor specific. We have known for several years that hyperplasia of the thyroid is present in most cases with a well developed clinical complex of Graves' disease; that marked hyperplasia is seldom noted in the thyroid except in patients having Graves' disease, and that exophthalmos is but rarely associated with any type of goitre except the hyperplastic. In each year of our series, in fact, in all reported series, there have been sufficient exceptions to the above rules to cause doubt in definitely associating the toxic symptoms, exophthalmos and hyperplasia of the thyroid. In going over my statistics for the last

five consecutive years I find that exceptions to the above rules have gradually diminished. This has come about from a clearer conception of the clinical pictures that may accompany hyperplasia and "simple goitre" (adenoma and diffuse colloid).

"The statistics of operation at the Mayo Clinic seem to warrant these conclusions: (1) that hyperplasia of the thyroid never exists without a production of thyroid secretion in excess of the demands of the individual; (2) that exophthalmic goitre is a clinical entity associated with a definite pathologic process in the thyroid; (3) that, if hyperplasia of the thyroid is of a sufficient degree or extends over a long enough period, exophthalmos is almost sure to develop; (4) that no matter how intense the intoxication from an adenomatous or colloid goitre not associated with hyperplasia, exophthalmos will not develop. Patients having simple goitre noticed the goitre at the average of 22.8 years, the evidence of intoxication at 36.6 years and came to operation at 39.6 years. That a patient 23 years of age having an adenoma has a definite fixed chance of developing thyrotoxicosis during her thirty-seventh year and that the symptoms may so closely resemble the clinical complex of Graves' disease that the two cannot be distinguished is one of the strongest arguments in favor of the latter disease being directly due to a disturbance of the function of the thyroid."

In 1913 Wilson showed that in cases of exophthalmic goiter as defined and diagnosed by Plummer the thyroid always shows histologically typical parenchymatous hypertrophy and hyperplasia. Wilson, as well as other observers, has been unable, as yet, to find any consistent pathologic differentiation of adenomas that produce symptoms of hyperthyroidism and those that do not produce symptoms of hyperthyroidism.

Goetsch in 1916 emphasized the importance of the relative number of mitochondria in thyroid adenoma and stated the belief that they were more numerous in those adenomas causing symptoms of hyperthyroidism and that thereby a means was afforded of distinguishing pathologically between adenomas that produce hyperthyroidism and those that do not produce hyperthyroidism; this differential feature apparently is not confirmed by the data reported in his later papers. Goetsch (1916) is also of the opinion that there is a very different form of intoxication in thyroid adenoma from that found in true Basedow's disease and is in this respect in agreement with the position maintained and repeatedly emphasized by Plummer since 1911.

In addition to the two distinct clinical entities of adenoma of the thyroid with hyperthyroidism and exophthalmic goiter Plummer recognizes a small intermediate group. At operation the thyroid in these cases is found, on pathologic examination, to have beside the adenoma more or less typical areas of hypertrophy and hyperplasia of the parenchyma, varying between very

small intra-adenomatous or extra-adenomatous areas to a small adenoma embedded in a typical hypertrophic parenchymatous thyroid. A discussion of this group is reserved for a subsequent paper.

In the differential diagnosis of adenoma with hyperthyroidism and exophthalmic goiter it is obviously necessary to exclude definitely cases presenting the syndrome of neurasthenia, usually of the cardiac type, with many of the earmarks of hyperthyroidism, but in which no hyperthyroidism nor over-activity of the thyroid is actually present. The co-existence of an enlarged thyroid, often not distinguishable from those producing hyperthyroidism, renders the exclusion of many neurotic cases most difficult, and in certain instances impossible unless the basal metabolic rate is known. Many of these patients with normal basal metabolic rates give a definite reaction to the epinephrin sensitiveness test, as pointed out by Goetsch and by Woodbury. In our opinion a normal basal metabolic rate eliminates hyperthyroidism.

The determining points in the differentiation of exophthalmic goiter and adenoma with hyperthyroidism were presented by Plummer in 1913. These principle points were:

1. The difference in the average ages of the patients when the goiter was first noticed. Enlargement of the thyroid was noted from five to ten years earlier in life by the patients with non-hyperplastic goiter than by the patients with hyperplastic (exophthalmic) goiter.

2. The time elapsing between the appearance of the goiter and the onset of the hyperthyroid symptoms. In exophthalmic goiter the symptoms of hyperthyroidism followed the onset of the goiter within nine-tenths of a year, while fourteen and one-half years elapsed before the thyrotoxic symptoms appeared in the group of non-hyperplastic adenomas with hyperthyroidism.

3. The relative frequency of exophthalmos in exophthalmic goiter contrasted with its almost complete absence in non-hyperplastic adenomas with hyperthyroidism. Exophthalmos occurred in 87 per cent of the cases of true exophthalmic goiter with symptoms lasting more than two years. It was less frequently present in the early stages of exophthalmic goiter, averaging 50 per cent in cases of less than three months' duration. In contrast, exophthalmos, even of questionable degree, was only rarely noted in cases of non-hyperplastic adenomas with hyperthyroidism. It

did not occur in any of the twenty-five cases of most intense intoxication in which operation was done in 1912.

An immense mass of evidence of the differences in the average blood pressures of the two syndromes has been collected by Plummer. A brief resumé of this work published in 1915 demonstrated a definite tendency to hypertension in adenoma with hyperthyroidism which is not found in exophthalmic goiter. Finally, the differences between the clinical picture of exophthalmic goiter and non-hyperplastic adenoma with hyperthyroidism led Plummer (1916) to point out in a condensed but valuable article, the probability of a different etiology in the two diseases. The isolation of the active principle of the thyroid, thyroxin, in pure crystalline form by Kendall (Dec. 25, 1914) and the subsequent studies of its physiologic activities have been of the utmost importance to a true concept of exophthalmic goiter and of hyperthyroidism and hypothyroidism, but a discussion of this phase of the problem is beyond the scope of the present article.

Since 1914 Plummer has used as a working basis the following hypothesis: "The active agent of the thyroid gland is a catalyst that accelerates the rate of formation of a quantum of potential energy in the cells of the organism." In 1916 Plummer stated that "the thyroid plays an important part in metabolism and that the evidence of high metabolism dominates the clinical syndrome of hyperthyroidism; and further, that the rate of metabolism is dependent on the thyroid hormone and that this function is not specific for certain tissues but is common to all the cells of the organism." Shortly after Plummer's paper was read, an exhaustive review of the variations in the metabolic rate in goiter was published by DuBois (1916) with a comparative study of the methods of direct and indirect calorimetry in these disorders. DuBois showed: (1) that the measurement of the heat production gives the best index of the severity of the disease and of the effect of treatment; (2) that the specific dynamic action of protein and glucose is within normal limits; (3) that the methods of direct and indirect calorimetry agree within the limits of technical errors, and in consequence (4) that the law of the conservation of energy holds good in exophthalmic goiter. Simultaneously, Boothby demonstrated in Cushing's clinic at the Peter Bent Brigham Hospital that the basal metabolic rate determined by the comparatively simple gasometer method of

indirect calorimetry is of great value in the diagnosis and treatment of thyroid disorders. The result of Plummer's recognition of the clinical value of metabolic rate studies was the establishment at the Mayo Clinic of the Metabolism Laboratory by Boothby and Sandiford in March, 1917. In this paper I shall present a preliminary analysis of the symptomatology and basal metabolic rate studies in hyperthyroidism due to adenoma of the thyroid based on Plummer's conception of the disease.

SYMPTOMATOLOGY AND BASAL METABOLIC RATES

Definition.—Adenoma of the thyroid with hyperthyroidism is characterised by an increased basal metabolic rate excited by an excess of the normal thyroid hormone in the tissues. About middle age the adenomatous tissue after a considerable quiescent period gradually begins to furnish an excessive amount of the apparently normal thyroid hormone (thyroxin) and this produces the increased metabolic rate and intoxication clinically evidenced by nervousness, tremor, tachycardia, loss in strength and weight, and a tendency to hypertension, and in the later stages myocardial disintegration. The underlying cause or stimulus that activates the thyroid to adenomatous growth and oversecretion is not known.

Pathology.—A simple descriptive key for the classification of the surgical pathology of the thyroid which involved no assumptions as to the clinical interpretation was evolved by MacCarty in 1912; the present study is based on the reports from the laboratories of the Section of Surgical Pathology. The pathologic condition of the thyroid in the cases classified as adenoma with hyperthyroidism was diagnosed either single (or multiple) granular, necrotic, cystic (degenerated), fibrous, calcareous, hemorrhagic, or hyaline degenerated or degenerating fetal or colloid adenoma in a normal or colloid thyroid. To avoid confusion in this study, no cases are included in which the pathologist reported even the smallest amount of hypertrophic parenchymatous tissue either intra-adenomatous or extra-adenomatous.

Symptoms.—Seventy-seven per cent of the patients suffering from hyperthyroidism of thyroid adenoma on coming to the Clinic are more than 40 (the average age is 48) and give a history of having had a more or less hard nodular goiter for many years (the average is nineteen years). For a long period the adenoma causes no symptoms, except that locally there may be a slight

feeling of fullness and possibly a tendency to a globus hystericus. For two or three years previous to examination a gradual change in general health takes place; the patient becomes more nervous and excitable and in the early stages he may have even a feeling of unusual "well-being" and of over-enthusiasm for work which is coupled, however, with the inability to maintain for long either mental or physical effort. The patient speaks of a good appetite and thinks he should be gaining in weight, but does not do so; somewhat later he finds that in spite of his hearty eating he is losing weight and his endurance is markedly decreased. His skin becomes warm and moist with a tendency to perspire freely. He feels that his heart is beating faster and harder, his attention probably having been directed to it first on going up stairs; later he notices palpitation even when he is at rest. The blood pressure often shows hypertension. Rarely can a patient give a definite date of onset of these symptoms since they come on gradually and insidiously; in consequence they are elicited only by careful direct questioning. Usually about one year before the patient comes to the Clinic his symptoms become distinctly accentuated, and frequently the goiter enlarges. Later, a distinct increase in nervousness and mental instability, a moderate tremor, a marked loss in weight in spite of an increased appetite, and a loss of strength, and an increase in dyspnea on exertion necessitate a material modification in the patient's mode of life. The heart beats fast and hard although it may not equal the violence of the beats in exophthalmic goiter. In the older and more severe cases there is evidence of cardiac insufficiency with more or less edema of the legs and ankles, frequently accompanied by myocardial disintegration evidenced by irregular rhythm due either to premature contractions or auricullar fibrillation. Gastro-intestinal crises, exophathalmos, thrills and bruits of so frequent occurrence in exophthalmic goiter are characteristically absent.

This history, on anlysis, is found to be characteristic of the systemic effects that might be expected from an increased metabolic rate, for in such a condition as much work is thrown on the heart to maintain the volume of blood required by the patient at his moments of rest as is needed by the normal person at a slow walk. During his waking hours all the additional blood requirement of muscular effort must be superimposed on this

high basal level. It is no wonder that in the early stages there is cardiac hypertrophy that progresses to cardiac overstrain with dilatation and degeneration in the later stages, and that in spite of the ingestion of large amounts of food loss in weight and strength is progressive. Due to the gradual and insidious character of the onset of the hyperthyroidism, which causes the increased metabolic rate the heart first hyperthophies and only in the later stages gives evidence of cardiac decompensation and disintegration. Then, like the broken compensation of the athlete's heart, the cardiac failure may quite suddenly dominate the picture, and for the relief of these symptoms the patient consults the physician. Not infrequently the casual relationship of the goiter may even then pass unrecognized and the patient be treated for ordinary cardiac decompensation.

As the duration of hyperthyroidism is prolonged and the metabolic rate gradually increases the factor of increased functional demand, as pointed out by Willius, is supplemented by actual myocardial changes resulting from the presence of an excess of the thyroid secretion (thyroxin). The rapidity of myocardial disintegration from this point depends on several factors: (1) the intensity and rapidity of progression of the hyperthyroidism; (2) the age of the patient (the heart of a young patient better tolerates the hyperthyroidism); (3) the presence of preexisting heart disease; (4) the physical stresses and strains to which the patient is subjected, and (5) the presence of preexisting hypertension. A large number of seriously damaged hearts is found in cases of adenoma with hyperthyroidism because of the insidious onset of the hyperthyroidism and its occurrence in patients of middle age. The scope of this paper, however, does not permit a more detailed consideration of the cardiac phase.

Age of patients.—The average age of these 281 patients at the time of examination was 47.6 years.

Patients under 20	4	(1.4 per cent)
Patients between 20 and 29	20	(7.1 per cent)
Patients between 30 and 39	41	(14.5 per cent)
Patients between 40 and 49	82	(29.1 per cent)
Patients between 50 and 59	92	(32.6 per cent)
Patients between 60 and 69	42	(14.9 per cent)

The average age of the 167 patients with adenomas without hyperthyroidism in whom the adenomas were of sufficient size to justify operation or for whom the operation was advised as a preventive against future hyperthyroidism was slightly younger, 43.8 years. This age, however, does not represent the average age of all patients with adenomas without hyperthyroidism who came to the Clinic, because for small adenomas without symptoms which occur in young persons operation is rarely advised. Exophthalmic goiter brings the patient to the Clinic, as a rule, ten years earlier in life than does the hyperthyroidism due to thyroid adenoma; in the four groups of cases of exophthalmic goiter (thirty-six, fifty-five, fifty-two, and fifty-two cases) in which the metabolic studies were made the average age of the patient at the time of the examination was 35.0, 36.7, 38.0 and 33.0 years, respectively.

Duration of goiter.—The time elapsing between the appearance of the goiter in adenoma with hyperthyroidism and the arrival of the patient at the Clinic was 17.9 and 19.7 years in the two groups. In a series of 167 cases of adenomas without hyperthyroidism that came to operation the duration of the goiter was slightly less, 16.9 years. In marked contrast to this is the duration in the four groups of exophthalmic goiter in which the patients had known of the existence of a goiter for only 2.8, 3.0, 3.5 and 3.2 years on the average, respectively. When from the averages of these groups the patients who had had goiter for more than five years are excluded the the average duration is 1.6, 1.0, 1.1 and 1.4 years, respectively. These patients may be rightly excluded because they had had either former exacerbations of exophthalmic goiter or a previously existing adenoma.

Duration of symptoms.—The duration of symptoms of hyperthyroidism before the patient comes to the Clinic is distinctly longer in cases of adenoma with hyperthyroidism than in cases of exophthalmic goiter. In the two groups of the former the length of time was 2.0 and 2.2 years, while in the latter the duration in the four groups was 1.6, 1.4, 1.7 and 1.3 years, respectively; however, if from these groups of exophthalmic goiter those cases are excluded in which the duration of the goiter was five years or more the average duration of symptoms is 1.3, 1.0, 1.3

and 1.0 years, respectively. The significant point is that the adenomas do not produce hyperthyroidism on the average for 15.9 and 17.5 years after their appearance while in exophthalmic goiter the symptoms of hyperthyroidism usually occur either coincidently with the appearance of the goiter or within a few weeks or months thereafter. Furthermore, the onset of symptoms in adenoma with hyperthyroidism is gradual and indefinite, while in exophthalmic goiter the patient not infrequently can even name the day of onset.

Blood pressure.—A complete analysis of the blood pressure readings will not be attempted in this paper; only a few salient points will be mentioned. The systolic blood pressure averages distinctly higher in adenoma with hyperthyroidism than either in the adenomas without hyperthyroidism or in exophthalmic goiter. The diastolic blood pressure is distinctly higher both in adenoma with hyperthyroidism and in adenoma without hyperthyroidism than it is in exophthalmic goiter. These statements hold good both for "floor" blood pressures, taken in the office at the time of the general examination while the patient is sitting, and for blood pressures taken when the patient is lying down, although the characteristic differences are emphasized in the blood pressures taken during the excitement of the physical examination. Many factors must be considered in a study of the significance of blood-pressure readings, the chief of which are the size of the peripheral cross-section and the amount of blood being driven through the periphery in a unit of time. It is evident that as a result of the increased metabolic rate both in adenoma with hyperthyroidism and in exophthalmic goiter the blood flow increases materially to meet the requirement of greater oxygen utilization while the patient is at rest. In the case of exophthalmic goiter there is an average high systolic blood pressure but a rather low average diastolic, giving a high pulse pressure; this combination coupled with an increased blood flow, indicates a relatively open periphery. On the other hand, the higher systolic and higher diastolic with increased blood flow in adenoma with hyperthyroidism indicate the association of definite hypertension. Likewise, in adenoma without hyperthyroidism the high diastolic with an increased systolic, but to a comparatively less degree, together with a normal blood flow also indicates an associated hypertension. Furthermore, there

TABLE 1.

Average Metabolic Rate and Blood Pressure in Adenoma and

	Adenoma						Exophthalmic			
	Without Hyperthyroidism			With Hyperthyroidism			Two ligations, 2 Months'			
Number of cases averaged in each group	167	18		201	75		36			
Age, years	43.8			47.7	47.4		35.0			
Duration of Goiter, years	16.9			17.9	10.7		2.8	(1.6)*		
Age at Onset of Goiter, years	26.9			29.8	27.7		32.2	(33.4)		
Duration of Symptoms, years				2.0	2.2		1.6	(1.3)		
Age at Onset of Symptoms, years				45.7	45.2		33.4	(33.7)		
Systolic B. P.	143			156	160		147			
Diastolic B. P.	85			86	86		73			
Pulse Pressure } On the Floor	58			70	74		74			
Pulse Rate	91			102	113		126			
Haemoglobin	75			73	74		70			
B. M. R.	+2	−4	−8	+28	+35	+7	+66	+50	+42	+19
Systolic B. P.	127	118	118	143	146	134	140	133	132	126
Diastolic B. P.	77	76	72	80	81	79	77	72	73	75
Pulse Pressure } At Time of Test	50	42	46	63	65	55	63	61	59	51
Pulse Rate	78	74	72	97	102	80	122	115	108	93
Weight							51.7	48.1	55.8	
	Before Treatment	Before Treatment	Two Weeks After Thyroidectomy	Before Treatment	Before Treatment	Two Weeks After Thyroidectomy	Before Treatment	Ten Days After Second Ligation	After 2 Months' Rest	Two Weeks After Thyroidectomy

*The cases in this group of more than five years' brackets because the duration of the goitre is confused

is a greater difference between the average floor systolic blood pressure and the average resting systolic blood pressure both in adenoma with hyperthyroidism and in adenomas without hyperthyroidism (13 mm., 14 mm., and 16mm.) than in exophthalmic goiter (7 mm., 8 mm., 8 mm., and 9 mm.), indicating the tendency to hypertensive contraction of the vascular tree. These facts led Plummer, in 1915, to state that adenoma of the thyroid both with and without symptoms of hyperthyroidism is frequently associated with vascular hypertension, causing a relatively contracted periphery, while in exophthalmic goiter, although the systolic pressures are high, there is no hypertension of the arterial tree but rather a relatively open periphery.

Basal metabolic rate.—A study of the basal metabolic rate brings out several very interesting facts, especially from the practical standpoint. Two distinct groups of adenomas of the thyroid have the same pathology, but one group is characterized

TABLE 1.

Exophthalmic Goiter Before and After Treatment

Goiter																				
Rest and Thyroidectomy						One Ligation and Thyroidectomy									Thyroidectomy					
	55					52						22			52					
36.7						38									33					
3.0	(1.0)					3.5	(1.1)								3.2	(1.4)				
33.7	(35.7)					34 5	(36.9)								29.8	(31.6)				
1.4	(1.0)					1.7	(1.3)								1.3	(1.0)				
35.3	(35.7)					36.3	(36.7)								31.7	(32.0)				
148						148									142					
75						76									78					
73						72									64					
124						121									121					
71						74									74					
+66	+42	+16				+52	+15					+57	+41	+16	+36	+8				
140	134	129				140	124					138	124	120	133	122				
74	71	76				73	75					72	64	73	72	73				
66	63	53				67	49					66	60	47	61	49				
122	109	90				113	90					116	109	92	109	88				
49.2	53.9																			
Before Treatment	After Second Ligation and 2 Months' Rest	Two Weeks After Thyroidectomy				Before Treatment	After 1 Ligation and 2 Weeks After Thyroidectomy					Before Treatment	Ten Days After 1 Ligation	Two Weeks After Thyroidectomy	Before Treatment	Two Weeks After Thyroidectomy				

duration are omitted from the averages given in the
by a pre-existing adenoma.

by hyperthyroidism with an increased basal metabolic rate and the other group presents no definite evidence of hyperthyroidism and the basal metabolic rate is within normal limits. The clinical histories of these two groups show a gradation from the adenoma with hyperthyroidism into the adenoma without hyperthyroidism both in the number and intensity of the symptoms that point to hyperthyroidism and in the lower basal metabolic rate. However, there is a change in the general character of the history and a distinct difference in the impression made by the patient on the examiner in the group of patients with adenomas and a basal metabolic rate above + 10 per cent and those with rates below + 10 per cent. Although in an individual case a reading of + 9 per cent or + 11 per cent or even between + 8 per cent and + 12 per cent does not absolutely determine the presence or absence of hyperthyroidism, if on a check reading the basal rate persistently remains above + 10 per cent fewer

clinical errors will be made if such readings are accepted as positive of mild or beginning hyperthyroidism and those with rates below + 10 per cent as not indicating hyperthyroidism. Patients having simply neurasthenia, even those whose symptoms most closely simulate hyperthyroidism, do not have persistently elevated basal metabolic rates. On the other hand, occasionally a normal metabolic rate is found in a case of quiescent hyperthyroidism either from exophthalmic goiter or adenoma that may be misleading unless attention is paid to the history of the disease carefully elicited from the patient. Such findings instead of decreasing the value of the metabolic rate really increase its practical value just as a normal or nearly normal temperature does in remittent or intermittent febrile diseases. On the other hand the number of these cases is very small and does not include the large group of neurasthenics who give a positive epinephrin reaction, but who have normal basal metabolic rates. We have found no evidence that this group of neurasthenics with normal basal metabolic rates, although they have some of the symptoms resembling those of mild hyperthyroidism, is dependent on variations in the physiologic activity of the thyroid gland, as suggested by Goetsch.

Technical errors of material magnitude in a properly conducted laboratory for routine work occur in less than 1 per cent of the cases. A moderate elevation of the metabolic rate sometimes occurs from the fear of the patient in submitting to the test. This is of practical significance, however, only in the borderline cases and therefore a check rate on a subsequent day should be obtained in patients whose first rates are between + 10 per cent and + 20 per cent before a final conclusion is reached. An elevated temperature curve due to a cold, sore throat, incipient tuberculosis or other cause raises the basal metabolic rate; the temperature curve at the time of the test must be known, therefore, because the febrile diseases as a group give an increased metabolic rate.

In adenoma with hyperthyroidism the curative effect of partial thyroidectomy (frequently simple enucleation of the adenomateous mass) is very strikingly shown by the drop in the basal metabolic rate within two weeks after thyroidectomy: the average metabolic rate fell from + 35 per cent to + 7 per cent or well within normal limits. In 67 per cent of the cases tabulated it

returned to normal within two weeks after operation; in 80 per cent it dropped to below + 15 per cent, in 92 per cent to below + 20 per cent, and in all the cases to below + 30 per cent. Plummer has frequently pointed out that thyroidectomy almost immediately cures the patient who has hyperthyroidism from adenoma and that recurrence does not follow unless a new adenoma or parenchymatous hypertrophy develops in the remaining gland. This is in contrast with the results obtained from thyroidectomy in exophthalmic goiter. Even in the mild cases of exophthalmic goiter with an average basal metabolic rate of + 36 per cent before operation which dropped to + 8 per cent after thyroidectomy only 45 per cent are within normal limits at the end of two weeks, although 76 per cent are below + 15 per cent. In a more severe type of exophthalmic goiter in which it was necessary to precede the thyroidectomy by a single ligation the average metabolic rate fell from + 52 per cent to + 15 per cent after operation; only 38 per cent of these were within normal limits and only 52 per cent below + 15 per cent. The improvement from a single ligation is shown in the average of twenty-two cases in which the average metabolic rate before treatment was + 57 per cent, and after the single ligation + 41 per cent; after thyroidectomy the average metabolic rate dropped to + 16 per cent. The first of two groups of the most severe type of exophthalmic goiter in which two ligations were performed and, after from two to four months rest at home, thyroidectomy was done showed an average metabolic rate obtained before treatment of + 66 per cent; after the second ligation and just before the patient went home the average metabolic rate was + 50 per cent; on return after prolonged rest at home the average metabolic rate was + 42 per cent, and after thyroidectomy it dropped to + 19 per cent. In the second group, similar to the first except that no metabolic rate was obtained directly after the second ligation and before the patient went home, the average metabolic rate before treatment was + 66 per cent; after the two ligations and approximately three months' rest at home the average metabolic rate was + 42 per cent and finally, after thyroidectomy, the average metabolic rate was + 16 per cent. The basal metabolic rate in only 36 per cent of the patients with exophthalmic goiter who had two ligations, rest at home, and thyroidectomy

returned to within normal limits two weeks after thyroidectomy; in 21 per cent it was still above + 30 per cent.

The metabolic rates in exophthalmic goiter will not be discussed in this paper, except to point out that after thyroidectomy: (1) the degree of hyperthyroidism is materially decreased; (2) the improvement, especially in the more severe cases is not so rapid or complete as in adenoma with hyperthyroidism; and (3) hyperthyroidism may still persist in certain cases and necessitate a second, and, rarely a third thyroidectomy.

SUMMARY

1. According to Plummer's classification there are two separate and distinct types of hyperthyroidism, each due to a different pathologic change in the thyroid gland: in the one type, the hyperthyroidism associated with the clinical syndrome of true exophthalmic goiter is always accompanied by diffuse hypertrophy and hyperplasia of the thyroid gland, in the other type the hyperthyroidism, not associated with this typical diffuse hypertrophy and hyperplasia, but with the occurrence of adenoma in the gland, is due to the adenoma, and the resulting clinical syndrome is distinguishable from that occurring in true exophthalmic goiter.

2. The syndrome associated with the hyperthyroidism from adenoma of the thyroid is considered by Plummer to be a distinct clinical entity and may be defined as a disease associated with adenoma, characterized by an increased basal metabolic rate excited by an excess of the normal thyroid hormone in the tissues. About middle age the adenomatous tissue gradually begins to furnish an excessive amount of the apparently normal thyroid hormone (thyroxin) and this produces the increased metabolic rate and intoxication clinically evidenced by nervousness, tremor, tachycardia, loss in strength and weight, and a tendency to hypertension, and in the later stages myocardial disintegration. The underlying cause or stimulus that activates the thyroid to adenomatous growth and over-secretion is not known.

3. Detailed metabolic rate and blood pressure studies are reported in seventy-five cases of adenoma with hyperthyroidism in which the average basal metabolic rate before treatment was + 35 per cent and after operation + 7 per cent. Similar studies of 201 cases before treatment are also given in which the average

basal metabolic rate was + 28 per cent. In contrast the average basal metabolic rate in 167 cases of adenoma without clinical evidence of hyperthyroidism was + 2 per cent; in eighteen of these cases the average basal metabolic rate before operation was — 4 per cent and it remained practically unchanged, — 8 per cent, as a result of thyroidectomy.

4. Three groups of exophthalmic goiter cases of varying degrees of severity were studied. In thirty-six patients with the severest type of the disease the average metabolic rate before treatment was + 66 per cent; these patients were subjected to rest in bed and two ligations at an interval of a week or more and within ten days after the second ligation the basal metabolic rate

TABLE 2.

Improvement Following Operative Treatment

B. M. R.	Adenoma with Hyperthyroidism after Thyroidectomy		Exophthalmic Goiter					
			After Thyroidectomy		After 1 Ligation and Thyroidectomy		After 2 Ligations, Home and Thyroidectomy	
	Percent below	Percent above	Percent below	Percent above	Percent below	Percent above	Percent below	Percent above
+10	67	33	45	55	38	62	36	64
+15	80	20	76	24	52	48	48	52
+20	92	8	91	9	67	33	59	41
+30	100	0	96	4	87	13	79	21
+40			100	0	94	6	87	13
+50					98	2	97	3
+60					100	0	100	0

was + 50 per cent. After three months' rest at home these patients returned to the Clinic and were found to have an average basal metabolic rate of + 42 per cent, with corresponding clinical improvement; within two weeks after thyroidectomy the rate had dropped to + 19 per cent. In a second group, fifty-two moderately severe cases, the patients were subjected to a single ligation and thyroidectomy one to two weeks later. The basal metabolic rate before treatment was + 52 per cent. after thyroidectomy + 15 per cent. In twenty-two the basal metabolic rate before treatment was + 57 per cent and ten days after the preliminary ligation was + 41 per cent; within two weeks after thyroidectomy the basal metabolic rate in this group had fallen to + 16 per cent. In fifty-two patients with mild exophthalmic goiter on

whom a primary thyroidectomy was performed the average basal metabolic rate before treatment was + 36 per cent and two weeks after operation + 8 per cent.

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A CASE OF DYSTROPHIA ADIPOSOGENITALIS

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Two considerations have impelled us to report the following case of dystrophia adiposogenitalis. One of the outstanding characteristics of the condition in question is a more or less pronounced psychotic trend. The subjects are frequently introverted and have a more or less pronounced inferiority complex. Timme has recently emphasized this fact. There are in the literature, however, relatively few cases reported with regard to psychopathological features. A second consideration is the desirability of more data on the therapeusis of the condition.

The patient, E. O'F., male, age 16, was first seen in the dispensary, January 28th, 1920. At that time plans were made to keep him under observation while undergoing treatment for his endocrine disorder. As a matter of fact, he proved to be a recalcitrant patient and it was only with difficulty that sufficient co-operation was obtained to permit carrying out a diagnostic and therapeutic study. For this reason the data reported are deficient in certain particulars,—and especially as regards basal metabolism and blood sugar determinations.

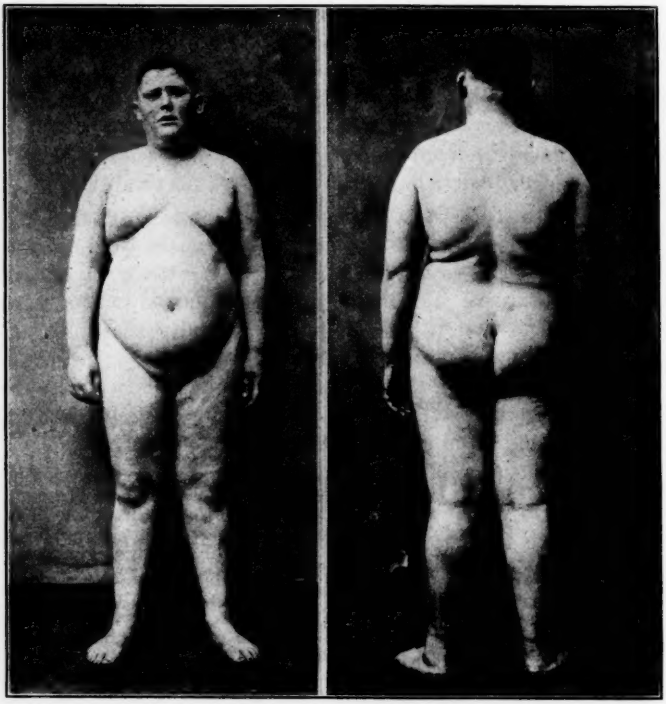
Family History: One grandfather was inebriate. The mother, now 50 years of age, is short, stout and has gradually gained in weight for the past 15 years. She stated that all her family have the same tendency toward obesity. Otherwise, the family history afforded no pertinent data. There is no evidence in the family strain of gigantism, dwarfism, goitre, or diabetes.

Personal History: The patient was born in Baltimore, March 12th, 1904. The mother "felt poorly" during her entire pregnancy; she had frequent attacks of dizziness and often refused food. She suffered much discomfort from what seemed like a lump in her neck. The patient was a full-term child, and except for his being undersized, his early development was normal. Breast feeding was continued until his third year and weaning was accomplished with some difficulty. The patient slept with his mother up to the time he came to the clinic. Since the age of 10, the patient has become exceedingly obese, this having become especially noticeable in the past three years. During this latter period he has grown in height 3½ inches. He had enuresis until the age of 4, but rarely since. He never has had night terrors. He has had the usual childhood diseases, including measles and chickenpox.

The patient did fairly satisfactory work in school from the 6th to the 15th years, reaching only, however, the high 5th grade.

He has always enjoyed good general health. There has been no complaint of headache or dizziness; no visual complaints; no difficulty of any of the special senses. During the past 5 years the patient has complained of dyspnoea on exertion, which has advanced in proportion to his obesity. There have been no gastro-intestinal complaints except occasional nausea and vomiting and an inclination to constipation. The appetite is excessive.

The patient states that he usually urinates from 5 to 7 times a day, and there is some hesitancy. Nocturia has been absent.



Photographs of patient, E. O'F., showing genital infantilism, distribution of fat, lumbar lordosis and genu valgum.

Present Illness: The patient resents teasing, is inclined to be infantile, cries on the slightest provocation, and is inclined at times to be over-affectionate. He has frequent spells of irritability. His employer states that he appears bright and alert in the morning, but is dull, obtuse, and complains of feeling tired "all over" in the afternoon. At home, it is noticed that the patient is over-affectionate, especially in regard to his mother. He is very obstinate and sullen at times. He

takes little interest in his work and gets along poorly with his associates on account of his sensitive and quarrelsome nature. The patient is ashamed of sleeping with his mother and is afraid that someone outside may discover it and make fun of him.

Recently he has shown an increasing tendency to be quarrelsome, irritable and stubborn. He shows little initiative in his work, is rarely punctual, and is inclined to lie to his employer.

He has a fair range of activities; goes swimming with other boys and plays baseball, although he feels handicapped and sensitive on account of his obesity and lack of genital development, about which he constantly worries.

Recently, his mother has been very much concerned regarding the increasing frequency of his crying spells, his marked infantilism and his complaints of weakness and tired feelings, especially marked in the evenings.

Mental Status: The patient is markedly infantile in his general demeanor. He is apprehensive, especially when any special tests are made, and cries when the finger is pricked. He talks in a well-modulated, high-pitched voice, and impresses one as being stupid. Point scale estimate of mental age by Dr. Scott reveals that of 10½ years: the intelligence coefficient is .77.

Physical and Endocrine Status: The patient is 5 feet 1½ inches in height and weighs 162 pounds. He presents a striking appearance with special reference to distribution of fat and rudimentary condition of the genitals. The deposits of fat are especially marked in the mammae, which are large and pendulous. He has a marked protruding and over-hanging abdomen, a large pad of fat just above the symphisis pubis and across the buttocks. The thighs are large, graceful and tapering. The pelvis is broad, suggesting the feminine type. He exhibits genu valgum and there is a slight degree of lumbar lordosis.

Measurements in the various planes of the body are as follows:

In the planes of the nipple		96 cm.
Planes of umbilicus		106 cm.
Planes of trochanters		102 cm.
At the internal malleolus, right and left		23 cm.
10 cm. above internal malleolus	right	26.2 cm.
	left	26.0 cm.
20 cm. " " "	right	35.0 cm.
	left	35.5 cm.
30 cm. " " "	right	38.0 cm.
	left	39.0 cm.
40 cm. " " "	right	47.5 cm.
	left	47.7 cm.
50 cm. " " "	right	54.0 cm.
	left	54.0 cm.
60 cm. " " "	right	60.0 cm.
	left	59.0 cm.
At the styloid process of ulna	right	17.5 cm.
	left	17.2 cm.
10 cm. above process of ulna	right	24.0 cm.
	left	23.5 cm.
20 cm. " " " "	right	25.5 cm.
	left	25.0 cm.
30 cm. " " " "	right	28.5 cm.
	left	28.0 cm.
40 cm. " " " "	right	34.5 cm.
	left	34.0 cm.
Sub-mental plane		51.5 cm.
Occipital mental plane		50.0 cm.

The skull is somewhat of the acromegalic type. There is a slight tendency towards prominence of the malar bone, and the lower half of the face is more prominent than the upper. There is a slight palatine ridge. The jaw is broad, with slight spacing of the teeth. The dates of dentition were not obtained, but the mother states that she thinks

there has been retardation of second dentition. The teeth are of normal color, shape and consistency.

There is a slight disproportion between size of the extremities and trunk. The torso-leg measurements are 46/80 cm. and the spread of arms, 56 cm. The hands and feet are small. The patient wears a no. 5½ shoe. The distance from the styloid of the ulna to the tip of the second finger is 18½ cm. A moderate degree of flat foot is present. The joints cannot be hyperextended.

Marked under-development of the genital organs is evident, corresponding to those of a boy 10 years younger. The penis is rudimentary and the scrotum is small and buried in fat. Both testicles are undescended. No evidence of puberal changes is found. There is no history of autoerotism or of any homo- or hetero-sexual trends. There is a marked deficiency of hair. This is especially marked in the axillae and pubic regions. On close examination, three short hairs are seen in the left axilla and four in the right. There is slight eyebrow deficiency. The hair of the head is fine and dry and has a slight tendency to curl. There is a marked ridging of all the nails. There is also a tendency to brittleness, and they crack readily. They are of slow growth. Several white spots are noticed, especially on the thumbs and the first and second fingers.

No abnormal areas of pigmentation were made out in the skin. It is thick and dry and shows no atrophy, naevi, or eruptions. There is a marked tendency toward "goose-flesh," especially marked on the arms and legs. There is a slight mottling of the face. On light stroking with the soft part of the finger tip, a red line is obtained with a broad, white border.

In the mucous membranes there are no abnormal pigmentations and no atrophy. The tongue is thick, with a normal number of papillae.

The patient shows a rapid muscle fatigability, especially during the skipping and hopping tests. When seen for the first time in the dispensary, after one hundred hops he complained of feeling exhausted and immediately rested on a couch. General weakness of all the muscle groups is present, but there is fair carriage.

The tonsils are small and atrophic. The axillary and inguinal lymphatic glands are not palpable. There is no thyroid enlargement detectable by palpation.

The systolic blood pressure is 140, the diastolic, 80. The pulse, at rest, is 68, standing, 80. The vessel walls show no sclerosis. The relative cardiac dullness measures 2½ x 10½ cm. There is no retromanubrial dullness. The heart sounds are of good quality and intensity, the second pulmonic being more marked than the aortic.

Blood examination shows:

R. B. C.—4,126,000.
Hemoglobin—75%
W. B. C.—8,960.

Differential Count:

P. M. N.,	64. %
P. M. E.,	1. %
Lymphs.,	26. %
L. M.	5. %
Trans.	3. %
P. M. B.,	.5%

The red cells are of normal size, shape and color. No parasites are found.

The urine is normal in constituents and shows normal range of specific gravity.

The radiographic examination shows an apparently normal sella turcica. In the bony structures there is delayed ossification for the age. The lungs are clear and no evidence of any mediastinal abnormality is detected. The teeth show nothing abnormal.

The perimeter chart shows normal visual fields for white, blue and green.

Treatment and Progress: Since the patient was unable to come into the hospital, arrangements were made with his employer to have him return to the dispensary at occasional intervals. The patient consented to return to the clinic for observation on Sundays. A resumé of his progress follows.

Beginning February 11th, 1920, he began to receive desiccated pituitary (whole gland, Armour preparation)—two grains, four times a day.

February 18th, 1920, the patient's mother reports that she has noticed that he shows less tendency toward weeping, is less irritable and stubborn, appears more active and alert, does not resent teasing as much as previously and sleeps better. He complains less of shortness of breath. He complains of frequency of urination, stating that he often urinates twelve and thirteen times a day; he also complains of frequent nocturia, three to five times a night.

February 20th, 1920, the patient states spontaneously that he is feeling better and stronger, has more vigor and does not notice the shortness of breath that he had previously. He ascends three flights of stairs and shows no abnormal degree of dyspnoea. He continues to complain of frequency of urination, but states that he has no nocturia.

February 25th, 1920, the mother states that the patient is more industrious, shows more initiative in work, is punctual, is sleeping better, is less irritable and has not had a crying spell for the past two weeks. Pituitary medication is increased to 12 grains a day.

March 3rd, 1920, the patient returns for observation and for blood and urine examination. While venous blood was being drawn he had a short fainting attack and crying spell. The next day he complained of dizziness while at work and was sent home by his employer. However, he was able to return the next day without any complaint. On March 4th, his mother states he had the first enuresis that was noticed since childhood.

March 10th, 1920, the patient's mother reports he has more self-confidence, shows more interest, is more buoyant at work and has no somatic complaints. He shows an increase in range of activities and is beginning to make plans with other boys in regard to preparations for a ball team. He appears less emotional, less infantile and associates more with boys of his own age. (Previously he has been in the habit of domineering the boys of his neighborhood five or ten years younger than himself.)

March 16th, 1920. The patient is becoming much dissatisfied because he is not losing any weight. In the hope of stimulating his catabolic processes, desiccated thyroid gland, 2 grains daily, is prescribed, the pituitary being reduced to 8 grains.

March 23rd, 1920. The pulse is 88 and blood pressure 140/85. The weight is 160 pounds and the temperature, 98.6°. There are no somatic complaints and no objective evidence of any tendency toward hyperthyroidism. The urine examination is negative.

March 27th, 1920. In the hope of stimulating genital development desiccated suprarenal gland, 4 grains a day is added to his other treatment. The patient's mother continues to note general improvement in his condition. She states that the boy is now walking home in half the time in which he did previously. He is getting along better

with his associates, and the people in the neighborhood notice a marked change in him, but the patient remains discontented since he has not been losing any weight.

March 28, 1920. The patient returns for observation. He shows his first loss in weight since treatment began, this amounting to two pounds. The pulse is 98; the blood pressure, 135/78. Measurement of the different planes of the body reveals a decrease of 4 cm. in the planes of the umbilicus, indicating a change in body configuration. The urine examination is negative. The differential blood count shows: P. M. N., 60.5%; P. M. B., 0.%; P. M. E., 1.%; Lymphs., 29.%; L. M., 5.5%; Trans, 4.%.

The patient exhibits a slight, fine tremor of the hand, but no other objective symptoms of hyperthyroidism. The von Graefe and all other eye signs are negative; there are no complaints of nervousness or palpitation; no vasomotor symptoms. The patient states that he urinates usually from five to seven times a day, but that he has lost all his former tendency to polyuria. His bowels move from two to four times a day. The patient thinks that he is getting along much better in his work, and he does not have any weak spells in the afternoon, as previously. He spontaneously mentions that all his friends and associates are very much surprised at the change in him. He mentions with some degree of ostentation that he can now walk home in thirteen minutes, when it previously took him twenty-five. He has no spells of shortness of breath. He is taking exercise regularly, playing baseball with more vim than ever before.

Subsequent to March the patient became increasingly less cooperative. During April, May and June, he received suprarenal, 12 grains, thyroid, 2 grains, and pituitary, 8 grains, daily. During this period his weight dropped from 162 to 152 pounds.

In June a slight growth of hair was apparent in the axillae and in the pubic region. No evidence of hyperthyroidism could be detected. He continued dissatisfied because there was no noticeable change in the size of the genitalia, although frequent erections were reported. Despite the medication, his basal metabolism at this time was found to be 4 per cent below normal. In view of the initial blood pressure finding of 140, careful observations were made at intervals to forestall any deleterious effects from the thyroid medication. An electrocardiographic examination at this time disclosed no abnormalities. There was no significant change in pulse rate or blood pressure. There appeared to be some further redistribution of fat, the diameter at the plane of the umbilicus decreasing 1.5 cm. more. At the same time the diameter at the plane of the nipples was augmented 2.5 cm.

During July, treatment was discontinued. During August, it was resumed in the same dosage as before. The patient, however, refused to return to the hospital for any further study. When seen at his home he stated that marked changes in his genital organs had occurred. He seemed apprehensive and complained that the medicine was "too strong."

On August 27th, 1920, he was seen for the last time. He refused to continue with any further treatment and was discharged. He was stubborn and self-assertive in demeanor, in striking contrast with his infantile behavior when first seen. He was working regularly, driving a two-horse team and earning twelve dollars a week. A striking change in the genital sphere was evident. Both testicles had descended. By palpation the diameter of each was estimated as 1.5 cm. The penis had increased somewhat in size, and the crines pubis and axillary hirci, although still scanty, were obviously augmented. The patient had developed a marked reticence as regards sex matters. He felt

alarmed at the genital changes. He continued to deny any autoerotic episodes and there was no evidence of heterosexual activity. There were no significant changes in blood pressure, pulse, or body measurements. The weight had again reached 160 pounds.

SUMMARY

A boy of 16 presented a case of dystrophia adiposogenitalis with psychic infantilism and marked fatigability. During the course of six months he was treated with desiccated pituitary, thyroid and suprarenal gland substance. At the end of the period there was a striking change in the psychic attributes from infantile to self-assertive stubbornness. He had become able to carry out a full day's work and to engage in vigorous athletics. At the same time the testicles had descended and erections were frequent. There was some growth of axillary and pubic hair.

DISCUSSION

To what extent should the psychic changes in the patient be ascribed to "desensitization" and suggestion, and to what extent to the medication? The data do not permit any very satisfactory conclusion. At the beginning of the treatment the prognosis, assuming that suggestive therapeutics alone were to be employed, could not have been at all favorable. Yet striking improvement, from a psycho-pathological point of view, did occur. The patient was transformed from a querulous, childish weakling to a robust lad, psychically fairly well adapted to his environment, and able to do a creditable day's work. He developed a keen interest in baseball and swimming and showed qualities of leadership.

The therapeutic plan carried out was not at all satisfactory as a scientific study. Each of the gland substances should, of course, from this point of view, have been administered independently and over periods of at least a year. In view of the uncooperative attitude of the patient, however, it seemed desirable to make the treatment as effective as possible, at once. The pituitary was administered on the supposition that the chief etiologic factor in the case was hypopituitarism. Favorable results from this alone seemed to appear promptly. The psychic attributes began to alter and the muscular fatigability to decrease. The thyroid was added in the hope that it would add to the patient's enthusiasm by augmenting a supposedly sluggish metabolism, and especially by leading to a decrease in weight. The fact that there was an initial systolic blood pressure of 140,

however, seemed to preclude any very vigorous pushing of the thyroid medication. As a matter of fact, the trend of the available literature seems to indicate that the addition of thyroid to pituitary material, on empirical grounds, is advisable in cases of the type discussed.

Whether the addition of suprarenal substance contributed to the therapeutic results, cannot be determined. That tumors of the adrenal cortex may cause an accentuation of the masculine characteristics is well known. Glynn has reviewed the literature on this point, up to 1912, in some detail. Apparently the therapeutic efficacy of the desiccated gland substance as a sexual stimulant has been but little investigated. Animal experimentation on the point has also received little attention. In 1916, one of us in collaboration with Augusta D. Hoskins reported the results of a preliminary study of the effects of suprarenal feeding in the white rat. The data, while not conclusive, numerically, seemed to indicate testicular hypertrophy as a result of the feeding. There is under way, at the Phipps Clinic, at the present time, a continuation of the study.

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DETERMINATION OF RELATIVE ACTIVITY OF THE THYROID LOBES.*

(With 3 figures in text)

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Muscular activity can be measured and recorded by means of a modern string galvanometer. The electrocardiograph gives a record of the cardiac mechanism by registering the changes in electric potential which occur with each phase of the cardiac cycle. Bayliss and Bradford in 1885 reported an investigation of the electrical changes attending glandular activity. Cannon and Cattell and later Gesell, have recorded the secretory action of the salivary and thyroid glands by placing one electrode of a galvanometer upon the gland and the other on neighboring tissues. They have offered evidence that the electrical changes are dependent upon variations in the activity of the glandular tissue itself. It is reasonable to suppose that the glandular activity of superficial glands, such as the thyroid, can be recorded by means of electrodes placed upon the skin directly over the glands.

In the electrocardiograph we have an instrument well adapted for such observations. The tension of the fibre can be adjusted to meet requirements and the resistance and standardizing currents can be utilized to regulate the deflection of the string. The camera makes possible a graphic record of the electric changes. In the following observations no attempt was made to measure the thyroid activity of one individual as compared with another but rather to estimate the activity of one lobe of the thyroid as compared with that of the opposite side. The procedure consists in attaching one electrode to the left leg or placing it on the back in the interscapular region, and placing the other electrodes on the right and left lobes of the thyroid, the second lead of the electrocardiograph being used for the right lobe and the third lead for the left lobe. Small German silver electrodes, ¾ inch square, were substituted for the ordinary electrodes used in obtaining a cardiographic record. The tension of the string was adjusted so that the deflections would fall within the photographic field. A record with an electrode placed on the manubrium was first made

*From the Medical Clinic of the Toledo Hospital.

in order to determine the deflection produced by the skin and body tissues, excluding so far as possible the influence of the thyroid gland. When a lobe of the thyroid was connected, with adjustments unchanged, the negative deflection increased. By changing "leads" without readjusting, the negativity of each lobe was compared with the manubrium and with that of the opposite side. The negative deflection was recorded photographically. The following observations have been made.

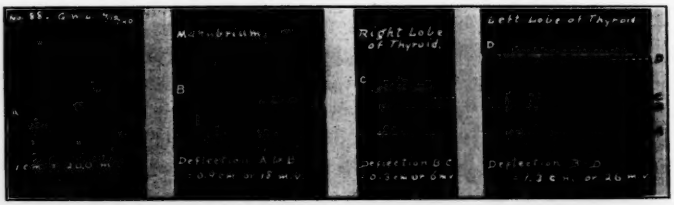

Fig. 1. (Reduced ½) Adolescent hypertrophy of thyroid with no evidence of thyrotoxicosis. Right lobe larger than left.
A-B=deflection produced by skin and other tissues.
B-C=additional deflection caused by right lobe of thyroid.
B-D=additional deflection caused by left lobe of thyroid.
The activity of the left lobe is greater than that of the right.

Case 1. (88) G. W. L. 4/12/20. Male, age 20. Adolescent hypertrophy of the thyroid gland with no evidences of thyrotoxicosis. The right lobe was larger than the left.

The tension of the string was adjusted to give a deflection of 1 cm. for each 20 millivolts. The lead from left leg to the man-

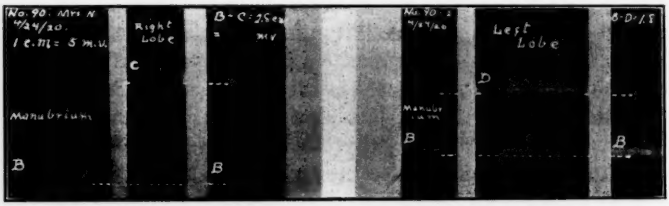

Fig. 2. (Reduced ½) Simple bilateral hypertrophy with normal basal metabolism. Right lobe larger than left.
B-C=deflection caused by including right lobe.
B-D=deflection caused by including left lobe.
The activity of the right lobe is greater than that of the left.

ubrium gave a deflection of 0.9 cm. The lead from left leg to the right thyroid gave a deflection of 1.2 cm., 0.3 cm. more than from the manubrium. The lead from the left leg to the left thyroid gave a deflection of 2.2 cm., 1.3 cm. more than from the manu-

brium. If this difference indicates the relative negativity of the two lobes we may state the condition in the following equation:—

Activity of right lobe: *activity of left lobe* :: *0.3 cm., 1.3 cm.*, and the right lobe, the larger of the two, is the less active.

Case 2. (90) Mrs. N. 4/24/20. Age 32. Moderate bilateral hypertrophy with no symptoms of hyperthyroidism and with a normal basal metabolism. The right lobe is slightly larger than the left.

One electrode was placed in the interscapular space, the two small electrodes upon the two thyroid lobes. The tension of the string was adjusted so that a deflection of one centimeter was equivalent to 5 millivolts. The difference between the deflection in leads from the manubrium and from the right thyroid was 3 cm. The difference between the deflection in leads from the manubrium and from the left thyroid was 1.8 cm. *Activity of right thyroid*: *activity of left thyroid* :: *3.0 cm.* : *1.8 cm.*, and the right thyroid, the larger of the two lobes, is presumable more active than the left.

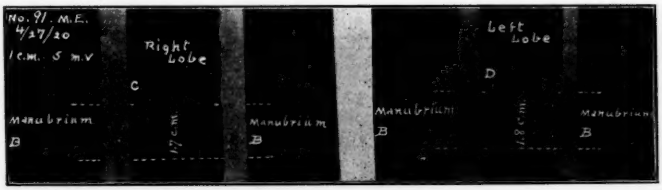

Fig. 3. (Reduced ½) Mild hyperthyroidism. Both lobes slightly enlarged.
B-C=deflection caused by including right lobe.
B-D=deflection caused by including left lobe.
The activity of the two lobes is equal.

Case 3. (31) 4/27/20. Mrs. E., Age 22. Slight bilateral hypertrophy of the thyroid with symptoms of a mild hyperthyroidism. The lobes are equal in size.

The tension of the string was so adjusted that 1 cm. deflection equaled approximately 5 millivolts. The difference between the deflection in leads taken from the manubrium and from the right thyroid was 1.7 cm. The difference between the deflection in leads taken from the manibrium and from the left thyroid was 1.8 cm. A second observation on this patient gave a deflection of 1.3 for the right lobe and 1.5 for the left lobe. The activity of the two lobes is presumably equal.

The three cases recorded, the first showing relatively greater activity in the left lobe, the second showing more in the right and the third showing equal activity, indicate that the application of this method may be of practical value. Our observations are too limited to do more than suggest a method by which the activity of the right and left lobes of the thyroid may be compared and graphically recorded.

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THE HYPOPHYSIS CEREBRI OF THE WOODCHUCK (MARMOTA MONAX) WITH SPECIAL REFERENCE TO HIBERNATION AND INANITION

(With 5 figures in text)

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CONTENTS

Introduction 33
Material and methods 38
Description of the hypophysis 43
a. General features 43
b. Pars nervosa 45
c. Pars anterior 45
d. Pars intermedia 49
e. Residual lumen 52
f. During hibernation 53
g. Post-hibernating period 54
Volume of the three parts 55
a. Before hibernation 55
b. During hibernation 56
c. After hibernation 57
d. Sex differences 58
Size of cells and nuclei 59
a. Pars anterior 59
b. Pars intermedia 60
Relative number of granular cells 61
a. Before hibernation 61
b. During hibernation 61
c. After hibernation 61
d. Significance of cell types 62
Summary 63
Literature cited 64

INTRODUCTION

In the thirty-four years which have elapsed since Marie created clinical interest in the hypophysis cerebri by associating disease of this organ with acromegaly, and especially during the last twenty-five years, or since Oliver and Schäfer (1895) announced that extracts of this ductless gland have a distinct power to increase general blood pressure, a vast amount of anatomical, physiological and clinical information has accumulated. Naturally this has been accompanied by various theories regarding the physiological role of this structure. One of these theories is that ordinary physiological sleep and the longer periods of dormancy seen in hibernating mammals are associated with activities of the

hypophysis. An examination of the principal observations upon which this idea rests may serve to place the subject in its proper setting.

In reviewing the literature on the theories of hibernation the writer ('16) called attention to the large number of authors who considered hibernation among the higher forms, at least, as merely an extreme form of ordinary daily sleep as seen in man and mammals. Hibernation, therefore, naturally suggested itself as being a favorable condition for investigating the factors involved in the production of sleep. Attention was also called to the views of Salmon ('05, '10) who argued that by virtue of some vasomotor or toxic power on the nervous system, the hypophysis is a center for the production of normal sleep . He discusses his theories again in 1916.

From the two preceding assumptions—(1) ordinary sleep and hibernation are merely degrees of the same phenomenon and (2) the hypophysis is a chief center in the production of sleep—Gemelli ('06) was led to a histological examination of the hypophysis of twenty-two adult European marmots (Marmota marmota). Some of these were sacrificed while hibernating and others during the active state in the spring and summer. He found no changes in pars nervosa (processus infundibuli) nor in pars intermedia (juxta-neuralis); but in pars anterior (distalis) a great reduction in the chromophilic cells during dormancy was observed—suggesting a stage of lessened activity. He, therefore, concluded that Salmon's view could not be correct because such a view involved a stage of hypersecretion on the part of the hypophysis during winter sleep. He further noted many mitotic figures in the spring after waking up. This would indicate that the time of greatest activity on the part of this organ was not during dormancy but after the animal becomes active.

The hypophyses of seven American marmots (Marmota monax), which like the European species have several months of profound dormancy (Howell '15), were examined microscopically by Cushing and Goetsch ('13, '15). Here particularly the hypophysis of hibernating animals was compared with that of the active animal of early spring. They interpret their findings as confirming in general the statements of Gemelli on the decrease in size of the whole organ and the loss of specific staining re-

action of the cells of pars anterior during winter-sleep. In their summary they state: "The gland not only diminishes in size, but the cells of the pars anterior in some animals at least completely lose their characteristic staining reaction to acid and basic dyes. At the end of the dormant period the gland swells, and as the cells enlarge they again acquire their differential affinity for acid, basic, and neutral stains and at the same time karyokinetic figures may appear" ('15 p. 46). They suggest that hibernation may be ascribed to a period of physiological inactivity possibly of the entire ductless gland series, but certainly more especially of the hypophysis. They cite clinical and experimental cases showing a distinct tendency to somnolence, storage of fat, subnormal temperature, slow pulse and respiration, lowered blood pressure and retardation of sexual development in hypopituitarism. One must agree that these symptoms suggest a tendency towards the conditions prevailing during winter-sleep of animals and that the tendency to associate certain forms of morbid somnolence with functional disturbances of the hypophysis (Dana '16) is well founded.

A far more extensive study of the ductless glands in relation to the onset of hibernation was carried out by Mann ('16) on the thirteen-lined ground squirrel (Citellus tridecemlineatus). From this study there was no suggestion of a distinct relation of the ductless glands to the production of lethargy. With reference to the hypophysis he found in some cases during dormancy a loss of the differential staining qualities of the granular cells of the pars anterior, some decrease in the size of the cells and an irregularity in their grouping. But these changes were inconstant and in several hibernating animals the hypophyses could not be distinguished from those of active ones.

The above summary shows that the results of Gemelli and of Cushing and Goetsch on the marmot as interpreted by them tend to show that there exists a stage of hypofunction on the part of the hypophysis during hibernation. The combined studies upon which this conclusion rests involve a total of twenty-nine animals. It appears, however, that the comparison was made largely between the dormant state and the active state following hibernation. It is clear, as pointed out by Mann ('16, p. 176) that the critical period is that just preceding hibernation. It is the conditions of this period that should be compared with those prevail-

ing during subsequent dormancy. This point is of special importance in animals that are sexually active only during the spring immediately after waking up, because of the probable close interrelation of the gonads and the hypophysis, a relationship which is generally accepted.

That there is some influence of the sex glands on the hypophysis rests largely upon the effects following castration and spaying. Observations on these effects (for review of the literature see especially Livingston '16, Addison '17a) are, however, conflicting. It appears that in the case of the albino rat Hatai ('13b) found it was only the male hypophysis that was markedly affected (enlarged) by gonadectomy. Addison ('17a) showed that this enlargement was accompanied by hypertrophy of the basophilic cells of pars anterior. Others have recorded enlargement of some of the other types of cells in a number of other animals. In the rabbit, Livingston ('16), who submits by far the most accurate data on this species, found no constant effect on the weight of the hypophysis by spaying and castration; while a more recent study on the rabbit by Hayami ('19) corroborates the findings of some of the earlier workers on this species by reporting hypertrophy of the hypophysis as a result of castration and of vasectomy followed by Röntgen rays treatment, the causal factor being the interstitial cells of the testis. Bell ('19, p. 195) also finds evidence of increased secretory activity in the anterior lobe and in pars intermedia after oöphorectomy in the cat, especially in regard to the eosinophilic cells.

The relationship of the gonads and hypophysis, as far as the influence of the latter on the former is concerned, is better established and is evident from the sexual disturbances accompanying disease of the hypophysis found recorded extensively in clinical literature. Extracts of the hypophysis, especially of pars anterior, are reported to stimulate the growth of the sexual glands (Goetsch and Cushing '13, Goetsch '16) although Hoskins ('16) and others (for a review of the literature see Hoskins' paper) fail to corroborate this. Such extracts are also apparently beneficial in some cases of sexual impotence (Stelwagen '16). Other generative structures are also influenced by the extract. This is particularly true of a stimulating effect on the mammary gland (Ott and Scott, Schäfer and Mackenzie, Herring, Gavin, Ham-

mond, Simpson and Hill, Gaines, Houssay and co-workers—literature well reviewed by Hill '16, Houssay '18).

While Cushing and Goetsch did not have the sexual glands from all their animals, they make the assumption that a very marked activation occurs in the reproductive organs when the animals emerge from the dormant state, "and it is tempting to attribute this to the influence of the functionally reactivated pars anterior" ('15, p. 41). In two previous publications the writer ('17, '18) has fully corroborated this surmise by describing the marked enlargement of the testes and ovaries which occurs during the spring awakening in the American marmot. These studies showed a suddenly increased activity both in spermatogenesis and oogenesis and a distinct hypertrophy of the interstitial cells at that time.

So it is obvious that a difference between the hypophysis of the hibernating period and that of the unusually active period immediately following, which is the rutting season, gives no valid evidence regarding the modification of the hypophysis during the dormant state. What occurs during this spring awakening is unusual activity following a long state of rest in most of the physiological processes but especially in those involved in the sexual cycle. It follows, then, that there is needed in the case of the marmot a careful comparison of conditions just preceding hibernation with those of lethargy in order to determine if there are significant structural changes detectable in the dormant animal. This apparently has not been made.

Finally all the data so far submitted are only roughly quantitative. The time has come, as has recently been emphasized by Hammar ('20), when it is necessary to extend anatomical data, particularly on the glands of internal secretion, upon a more accurate quantitative basis, in order to facilitate the making of reliable deductions from pathological and experimental material. Since there are at least three more or less distinct components (Tilney, '13, recognizes at least four) in this organ, each probably of different functional significance (most strikingly brought out recently by Allen '20), these several structures must be investigated. It is conceivable that one part might respond by hypertrophy and yet not be detected by the weight of the whole organ because of compensatory changes in another part, etc.

In view of these conditions and the failure of Mann ('16) to corroborate on another species the reported observations on the marmot, it seemed desirable to extend the inquiry by using more accurate quantitative procedure. There might, of course, be some differences in the way various species respond. It was also expected that histological findings in the hypophysis during the very active period immediately after waking up might give facts of importance regarding the response of the various cellular elements to this condition of hyperactivity, and thus add to our knowledge of the significance of the various types of cells described especially in pars anterior.

It is interesting to note that Saito ('19) has reported that in the horse the weight of the hypophysis varies with the month of the year.

MATERIAL AND METHODS

The material upon which this report is based consists of the hypophyses of thirty-two adult woodchucks from the vicinity of Ithaca, New York. Fifteen of these animals are among those studied for Nissl changes in nerve cells during hibernation (Rasmussen and Myers '16) and are known as Series I in my records. These fifteen and two additional animals (No. 1 and No. 2, Series II) taken together constitute a series of nine males and eight females. One male hypophysis was so damaged in the process of preparation that it was only of cytological value. Of the remaining sixteen perfect organs four (two from males and two from females) were taken before hibernation; four (two from males and two from females), during dormancy; five (three from males and two from females), after waking up but before being fed; three (one from a male and two from females), in the spring while active and after having been fed one, two and three weeks. The smallest male of the non-fed active group that was killed after hibernation, was not used in volumetric calculations, thus leaving in the three principal groups an equal number of each sex and thereby reducing the error due to sex-differences if such differences should exist.

All these animals were killed instantly by transfixing the heart quickly through the chest wall, in most cases without the use of any anaesthetic. Most of the blood was immediately washed out with physiological saline solution at body temperature by perfusion through the aorta. The saline was followed by a sat-

urated aqueous solution of bichloride of mercury to which had been added 10 per cent of formalin. The whole body was thus fixed very quickly while still warm or still cold depending upon whether the animal was active or was lethargic.

Following the removal of the brain, the hypophysis was carefully dissected out and further fixed for 48 hours in a saturated aqueous solution of bichloride of mercury. After washing in running water for 36 hours, the tissue was dehydrated as usual and imbedded in paraffin. The time intervals in the reagents were the same for all specimens so that the shrinkage ought to be very nearly the same in all cases. This point is of importance because the method of fixing *in situ* made it impossible to get the weight of the fresh gland as a check upon volumetric changes produced by the histological technique.

The above material was used for determining the volume of the whole organ and its different parts, the volume of cells and of nuclei, and for a differential count of the basophilic and acidophilic cells of pars anterior. Each hypophysis was cut into serial section 5 μ thick and mounted upon six slides. The plane of section was horizontal, i. e., through the greatest diameter, so as to decrease the number of sections and to present to the best advantage the three principal regions traversed. The first slide was stained with Delafield's hematoxylin and eosin; the second, with methylene blue and eosin; the third, with the aniline blue-orange G-phosphomolybdic acid mixture used in the well known Mallory's aniline blue connective tissue stain; the fourth, with acid fuchsin followed by the aniline blue and orange G mixture as regularly done in Mallory's connective tissue stain; the fifth, with Delafield's hematoxylin and acid fuchsin; and the sixth, with one of the preceding methods depending upon which stain needed checking.

Another series of hypophyses was available from the fifteen animals utilized in the study of the mitochondrial content of nerve cells during hibernation (Rasmussen '19) in the report of which the data concerning the animals are given. They are registered as Series IV and No. 51 and No. 56 of Series III. This material was fixed also *in situ* by injecting Regaud's fixer (one part of commercial formalin neutralized with magnesium carbonate and four parts of a 3% aqueous solution of potassium bichromate) after the blood had been washed out with oxygen-

ated Locke's fluid. The organ was dissected out and further fixed for five days in Regaud's mixture, changing the solution every day, and followed by 3% aqueous solution of potassium bichromate for nine days, changing the solution every day. This preserves the mitochondria well (Cowdry '16). The tissue was imbedded in paraffin with the same precautions exercised with the other material regarding equal duration by all samples in the various reagents including the paraffin bath. Serial sections were cut 5 μ thick until about halfway through the block. The block of tissue and the knife of the microtome were then further cooled by means of a piece of ice held against them. A known number of sections (from 20 to 30) only 2 μ thick were then cut. The rest of the block was cut 5 μ. This gave an uninterrupted series and at the same time enough very thin sections for more detailed study. The 5 μ sections were mounted on about six slides with the point indicated where the thinner sections belonged. Some were stained in hematoxylin and eosin and the remainder for mitochondria in Altmann's anilin fuchsin (20% acid fuchsin in anilin water) and a 1% aqueous solution methyl green (Cowdry '16). Knowing the number of 2 μ sections taken out of the series it was possible to use them for determining the volume of the whole gland and of its various parts since, as will be explained later, it is necessary to use only every tenth section. The 2 μ sections were mounted upon separate slides (three or four sections to a slide) and stained as above for mitochondria after various degrees of dechromation.

The fifteen hypophyses fixed by this second method represent five animals (three males and two females) in each of the first three stages represented by the material first described.

A difference in the fixation necessarily meant that the volumetric data had to be worked out separately for each lot of material. It was found, however, that the figures from each lot were between practically the same limits, dehydration and imbedding having apparently caused sufficient shrinkage to obliterate any differences that might have existed immediately after fixation. For a differential count of the cells of pars anterior only the first described material (formalin-corrosive sublimate fixation) could be used; for mitochondria, only the second (neutral formalin-potassium dichromate fixation). For the rest of the work both lots could be used, the volumetric data being thus

based upon thirty whole hypophyses—nine from animals killed before hibernation, between Sept. 4 and Dec. 3, rectal temperature 35°C—38°C; nine from animals sacrificed while dormant, between Feb. 3 and Mar. 18, rectal temperature 7°C to 16°C; nine from animals killed after waking up, between Mar. 16 and April 18, rectal temperature 34°C—37°C; three from animals having been awake several weeks without food and then having been fed one, two and three weeks, killed between April 5 and April 18, rectal temperature 36°C—38°C.

The method of determining the volume of the gland and its various parts as well as the size of cells and nuclei was the paper method of Hammar as used by Jackson ('17). The mathematical basis of this procedure is more fully explained in a later publication (Jackson '19). Suffice it to say that for determining the volume of the whole gland and of the various lobes every tenth section of the series was projected upon standardized paper by means of an Edinger projection apparatus at a magnification of 77 diameters and the various parts outlined, then cut out and weighed. Knowing the weight of one sq. cm. of paper, the surface area of each outlined area is obtained. This was reduced to actual area by dividing by the magnification (77^2) and then multiplied by the thickness (50 μ) represented by each of the selected sections to give the actual volume. There was left on the organ only an extremely thin fibrous capsule and since the lumen of the residual cavity (intraglandular cleft) and large cyst not containing colloid, or hyaline substance, were discarded when cut out, the weights represent essentially parenchyma and vascular stroma.

In determining the volume of cells and nuclei all the nuclei and vascular stroma in focus at the same time were traced within an area easily outlined by means of a camera lucida and at a magnification of 2100 diameters (Zeiss 2 mm. apochromatic objective, compensating ocular 8). The vascular stroma was cut out and discarded. The remaining paper, represented the essential parenchyma, was weighed. The nuclei were counted, cut out and discarded, and the paper (now representing cytoplasm only) again weighed. The difference between the two weights gives the nuclear area. From these figures and the known weight of a unit area of the paper, the magnification and the number of nuclei (which also represents the number of cells), the average volume

of the entire cell and of its nucleus were calculated. In the case of pars anterior this was carried out on four different regions on a section passing through the organ near its greatest diameter. These regions were selected from about the same positions in each case. These are indicated by the four crosses in figure 1. There is sufficient variation in the cells in different parts of the lobe and a fair degree of regularity in the positions where these differences are located to make this procedure necessary. Each of the four areas contained from 61 to 154 nuclei and the four together involved in the neighborhood of 300 nuclei. In pars intermedia only two fields were taken—one from about the middle of each lateral half as viewed in sections passing through the greatest diameter of the whole gland. The cells bordering the residual cavity as well as those next to pars nervosa were not included in the area outlined because these are invariably smaller (fig. 4) than those forming the main bulk of this lobe. In each field in pars intermedia 35 to 85 nuclei were outlined and the two fields together yielded in the neighborhood of 100 nuclei.

The method of cutting out the nuclear areas is of some consequence on account of the tedious task which it involves in an extensive research. Jackson used a sharp scalpel and placed the paper on a wax plate such as is used for reconstruction in the making of anatomical models. The wax plate renders cutting easy but small particles of the wax composition may adhere and if unnoticed produce an appreciable error. The main objection, however, is that it is fatiguing to the hand. While it is no quicker, it is much easier and just as accurate to cut out even the smallest nuclei by means of a fine manicuring scissors with increasing curvature toward the point. One can cut for hours without inconvenience. When a nucleus has been cut out a slit is made from the resulting hole over to the nearest nucleus, etc. When the paper becomes too frail one blade can be inserted into the outlined nucleus and the area excised without communicating with any other hole.

In making the differential count of cells in pars anterior only the granular or so-called chromophilic (acidophilic and basophilic) were enumerated—these being in the minority and the cells usually associated with active secretion. In each animal an entire section near the greatest diameter of the organ was explored systematically by means of a mechanical stage from side

to side, stopping for a count as soon as all parts of the previous area had passed out of the field of vision. A section explored in this manner yielded from 206 to 284 fields, with a total count of 8,759 to 13,086 acidophiles and 263 to 3,572 basophiles. To detect any distinct variation in the proportion of the three types of cells it was deemed sufficient to determine the average number of cells of the two types per field, since it had previously been found that there was no marked variation in the size of the cells taken as a whole, from which it follows that the average number of total cells in a unit area (say an entire microscopic field where the magnification, lenses, etc., are kept constant) would be the same in the different stages.

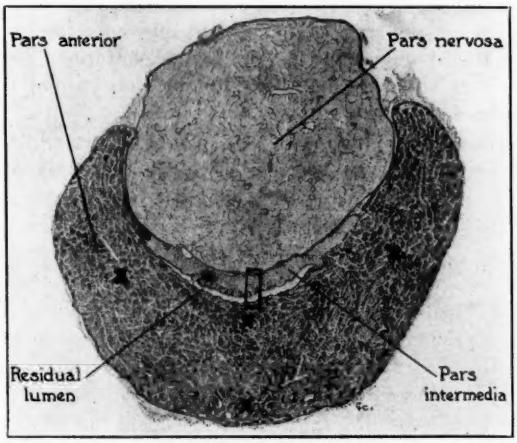

Fig. 1. Horizontal section through the hypophysis of the woodchuck at about the greatest diameter showing the general arrangement of parts. Formalin-corrosive sublimate fixation; methylene blue-eosin stain. X 20.

DESCRIPTION OF THE HYPOPHYSIS OF THE WOODCHUCK

a. General features

The main bulk of the hypophysis of the woodchuck (as already briefly described by Cushing and Goetsch '15) is a flattened disc from 3 to 4.5 mm. in diameter and from 1 to 2 mm. in thickness near the center and thinner towards all edges (dimensions obtained from the fixed material). It lies horizontally in a very shallow sella turcica. The glandular portion forms a distinct crescentic mass half encircling the nervous por-

tion, as shown in figure 1. The infundibular stalk is short and delicate and breaks readily close to the distal enlarged portion. Only in a few cases was much of the infundibulum and adjacent portion of the tuber cinereum retained. From these it appears that all the regions recognized by Tilney ('11, '13) are present. The infundibular stalk is solid through its greatest extent so that it belongs in Vincent's ('12) third class represented in man, monkey, ox, pig, rabbit, etc. It is accompanied by a thin layer of glandular tissue, two to four cells in thickness, continuous below with the main bulk of pars intermedia. The cytoplasm of the cells of this thin layer is much less abundant, the nuclei are slightly smaller and more nearly spherical and stain more deeply than in the cells which form the greater part of pars intermedia. The cells are arranged in anastomosing strands in a stroma almost as vascular as that of pars anterior. The extent to which they surround the infundibular stalk cannot be determined from the material at hand.

The thin layer of cells just described becomes thicker as it spreads out on the under surface of the eminentia saccularis of the tuber cinereum. Thus there is what Tilney terms a pars tuberalis in the juxta-neural glandular tissue. The extent of the pars tuberalis cannot be described here because not enough of the hypothalamus was retained in any case.

The part of the gland primarily investigated was only the enlarged disc-shaped portion consisting of processus infundibuli, which will be designated by the more familiar term pars nervosa; that part of the glandular pars infundibularis that is associated with processus infundibuli, which will be spoken of as pars intermedia; and pars distalis, or the main body of glandular tissue, which will go by the better known name of pars anterior. If additional structures were present they were excluded from the tracings. The point where the pars nervosa rather suddenly narrows down to become the infundibular stalk, a point which is also the upper limit of pars anterior, was taken as the upper boundary line and, therefore, only that portion of the gland below this level is included in the volumetric data. The naked infundibular stalk was always present above this line but pars intermedia usually broke at this point or slightly above except in a few cases where the line of separation was through the floor of the third ventricle. The structures included constitute, however,

the better known parts and by far the main bulk of the organ.

b. Pars nervosa

Pars nervosa is solid and pear-shaped, with the infundibular stalk representing the stem. In cross section it is nearly round (fig. 1). A very thin fibrous capsule covers the entire surface. There are no histological features that are either unique or of importance, but they conform to the general description given for other mammals. Fibers constitute the main bulk. It is well supplied with blood vessels. Small masses of homogeneous colloid-like material, somewhat larger than the cells present, are scattered about in all parts of the lobe. They lie free in interstitial spaces.

c. Pars anterior

Pars anterior is crescentic in shape and closes in around the lateral borders of pars intermedia so as to come in contact with

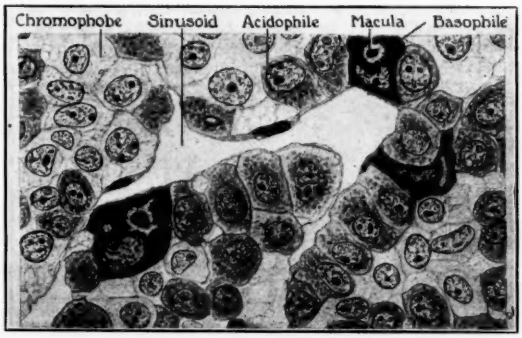

Fig. 2. Small area of pars anterior showing types and arrangement of cells. Formalin-corrosive sublimate fixation; Mallory's acid fuchsin-aniline blue-orange G connective tissue stain. X 1000.

pars nervosa (fig. 1). It is also invested with a delicate fibrous capsule. The cell arrangement is of the most common type, namely, irregular anastomosing cords separated by a rich system of sinusoidal capillaries (figs. 1 and 2). Nothing simulating acini was seen strictly within pars anterior.

The cells appear to be of three distinct types, usually termed chromophobes but also termed chief cells and reserve cells (lightly staining and devoid of many coarse granules), and acidophilic and basophilic chromophiles (staining intensely due to the presence in the cytoplasm of coarse granules which are either dis-

tinctly acidophilic or distinctly basophilic). As shown in figure 2 where the three types are shown in three tones of shading, there is a striking absence of intermediate forms. These three types of cells were found to stand out most clearly tinctorially with Mallory's acid fuchsin--aniline blue—orange G connective tissue stain after formalin-corrosive sublimate fixation. For a study of basophiles, as was also the experience of Addison ('17), omitting the acid fuchsin gives the clearest preparation with maximum contrast. The basophilic cells take the aniline blue and, therefore, stand out in great contrast against the yellow acidophiles and almost colorless chromophobes. However, the acidophiles are best seen when stained with acid fuchsin. As shown by Cooper ('19) it is the same cells that stain intensely yellow with orange G and intensely red with acid fuchsin.

The chromophobes are somewhat more numerous than the chromophiles. They form the body of the cords and, while often seen next to the capillaries, do not show much tendency to border on the blood channels. They vary much in size, a few being

Fig. 3. Cells from pars anterior showing the mitochrondrial content. Neutral formalin-potassium dichromate fixation; acid fuchsin-methyl green stain. X 1000.

among the larger cells encountered while most of the smallest cells are of this type. As has often been noted, the boundaries of the individual cell are difficult to make out with most stains. The mitochondria (fig. 3) are mostly granules ½ μ or less in diameter. Short rods are often seen and occasionally a rod as long as 2½ μ as well as comma-shaped mitochondria are observed. If the cytoplasm is scanty, the mitochondria may be reduced to a single perinuclear layer. The nucleus is of the usual type, either round or somewhat elongated, rather smooth in outline and containing from one to three nuclei and a fairly coarse chromatin network.

The acidophiles are somewhat less numerous than the chromophobes. They are, on the whole, slightly larger and show a

decided tendency to occupy the periphery of the cell cords so that they are mostly found directly in contact with the endothelium of the vascular channels (fig. 2). This arrangement has been repeatedly noted in other animals by various investigators. Uniform, round granules fill much of the cytoplasm, especially next to the nucleus. The margin being usually less densely packed with these acidophilic bodies, the limits of the individual cell are fairly distinct. In some of the larger cells there is a lighter colored area resembling a large vacuole in the interior of which is a body possessing the same staining properties and granules as the denser cytoplasm. Addison (17a, b) has discussed this structure under the heading "Golgi apparatus" and upon the basis of his work on the albino rat after castration considers it to be a definite cell organ. Gemelli ('07 and earlier publication listed in this reference) has also described large vacuoles and a Golgi reticulum in the chromophilic cells. In the woodchuck material here described this structure has been designated "macula"—the term tentatively applied by Addison ('17a). This structure is seen in the acidophiles best in the material fixed in neutral formalin-potassium dichromate and stained with acid fuchsin—methyl green, but even then only in a small percentage of the cells; although it is very likely present in a great many more, if not in all, but in a smaller and less conspicuous form. It is probable that with the technique used here it shows up only in the cells where the light zone has been greatly exaggerated by the action of the reagents. One of the largest and most conspicuous maculae observed in the acidophiles is sketched in figure 3.

Mitochondria are present in large numbers (fig. 3). They differ in no way from those already described. It is difficult to be sure of the relative number of mitochondria by the method here used because the large acidophilic granules also take the fuchsin stain and if dechromation is carried to the extent that these larger granules do not stain red, one cannot always be sure of having brought out all the mitochondria present. However, their small size and deep red color make their identity fairly certain even when the cytoplasm is still somewhat red.

The nucleus is slightly eccentric but in structure differs in no particular from that of the chromophobes.

The basophilic cells are least numerous, there being only about one of these to every ten acidophiles. Under usual conditions there is, however, a great variation between individual animals. In one case there may be as few as one basophile to about thirty acidophiles and in another animal as many as one basophile to three acidophiles (table 4). In nearly all cases they are more numerous towards the periphery of the lobe but not at the extreme edge. This peripheral distribution has been seen in other animals (Tilney '11), but denied by Jackson ('17) as a characteristic feature in the albino rat. They occur singly, as a rule, but where numerous may be in clumps so that the majority of the cells in a high power field of the microscope are basophiles. They show some tendency to occupy the regions next to the sinusoidal blood vessels. In outline they are more irregular and as shown in figure 2 may occupy irregular spaces between other cells. The largest cells met with are usually of this type, although there are many medium sized basophilic cells.

The cytoplasm is literally filled with coarse basophilic granules except for a conspicuous light ring or irregular space about a distinct macula, as described in the acidophiles. Practically every cell must contain such a structure, judging from the number of cells in which it is actually present in the section. Naturally a great many cells are so cut that the portion in a particular section does include the macula. This structure varies greatly in size, and to some extent directly with the size of the cell. In the largest cells it may be as large as the nucleus. In the smallest cells it may be smaller than the nucleolus. It is situated most often near the center of the cell. The light area about the macula and the macula itself may be greatly flattened as if by external pressure. While the surrounding vacuole-like region is usually fairly regular in outline, it may be very irregular and branched, as seen in the largest cell in figure 2. In very large cells an additional light area, variable in size, resembling a vacuole, is occasionally seen. The macula shows the same structures and staining reactions as does the dense cytoplasm outside of the light area.

The mitochondria are of the same form as those in the other cells but show a greater tendency to be arranged in rows. They appear less distinct on account of the denser cytoplasm. Probably for this reason they seem somewhat less numerous in proportion

to the amount of of cytoplasm than in the other two types of cells.

The nucleus is almost always very eccentric and is very frequently irregular in outline, with a tendency for the concave side to be next to the macula. Its structure does not seem to differ from that of the other nuclei.

As shown in figure 4, the cells of pars anterior which form the anterior wall of the residual lumen are distinctly smaller, more irregular in outline and stain more densely. In some sections these smaller cells form a two layered wall separated from the rest of pars anterior throughout the entire length of the cavity by a plexus of capillaries. These smaller cells are mostly chromophobic in general reaction.

d. Pars intermedia

Pars intermedia, as is clear from figure 1, constitutes a very small part of the hypophysis. Table 1 shows that it may form less than one per cent of the entire organ and is always less than four per cent. It consists of a lamina fairly uniform in thickness usually with a smooth posterior surface, which is closely applied to the thin capsule of pars nervosa. In four out of thirty cases, however, lobules of cells from pars intermedia invaded the neural lobe for a considerable distance. The residual lumen may follow along with this ingrowth. This encroachment of pars intermedia upon pars nervosa has been noted now and then by others. Herring ('08) in his description of the mammalian hypophysis states that this is most frequently met with in the region of the neck of the gland and that islets of epithelial cells may be found throughout pars nervosa. Cushing and Goetsch ('10) state that it is not uncommon in so-called normal human hypophyses, while Erdheim ('03) and Lucien ('09) found it more prevalent in advancing years.

Pars intermedia rarely comes to the external surface of the organ except at the most dependent point and of course along the hypophyseal stalk above pars anterior. Over half of its anterior border is separated from pars anterior by the residual lumen. There is a tendency for the intermediate lobe to surround the margins of this cavity and to form a little of its anterior wall. It extends some distance peripherally between pars anterior and pars nervosa beyond the hypophyseal cavity.

As is almost universally the case among animals, this part of the hypophysis is poorly provided with blood vessels. Almost no capillaries are seen in its interior. The posterior border is well supplied with vessels but they do not extend very far in the anterior.

The general histological features are shown in figure 4. It will be noted that four types of cells are present. The main bulk of the lobe is formed of cells which upon measurement (table 3) are seen to have about twice the volume of the cells of pars anterior. The abundant cytoplasm of these cells is devoid of many large granules and therefore, while rather basophilic in reaction, appears distinctly lighter than pars anterior and hence its limits can be readily ascertained by almost any stain. These cells are irregular in shape due to mutual compression. The central cytoplasm is denser and contains more mitochondria

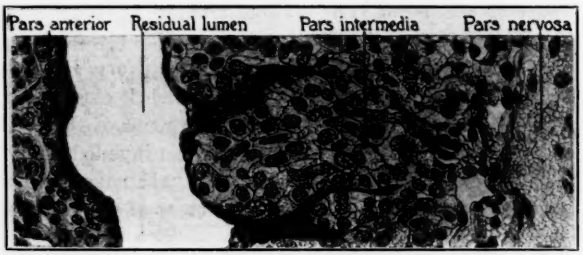

Fig. 4. Narrow strip through pars intermedia and a small part of adjacent pars anterior and pars nervosa. An enlarged view of the rectangular area outlined in figure 1. Formalin-corrosive sublimate fixation; methylene blue-eosin stain. X 400.

than the peripheral cytoplasm (fig. 5 B), which has the general appearance of being composed of more fluid areas separated by denser strands radiating from the central cytoplasm. According to Lewis and Maurer ('20) the lighter areas between the denser strands are filled with secretory antecedents.

The nucleus is usually eccentric in position, rather vesicular in appearance and round or more or less elongated in shape.

Along the posterior margin a variable number of cells occur which are much smaller and contain much denser cytoplasm and a heavier staining nucleus. They are responsible for the darker shading along the posterior boundary of pars intermedia in figure 1. In figure 4 their hyperchromatic nuclei are best seen

while figure 5 C is a sketch of three of these cells under higher power. The scanty cytoplasm is rich in mitochondria. The stratum which these cells form is not usually as wide as in the case illustrated in figure 4. It is as a rule more irregular in thickness, not being seen at all in places and in other limited areas being one-third as wide as the entire thickness of pars intermedia.

The anterior margin, which forms the posterior wall of the hypophyseal cavity, is lined by cells which may be either greatly flattened or high columnar as shown in figures 4 and 5 A. The columnar cells form groups which extend a variable distance into the substance proper—a great exaggeration of the tendency

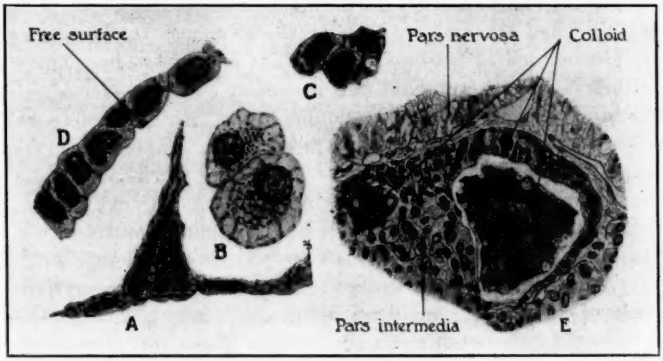

Fig. 5. Details from pars intermedia. The four small groups of cells show the mitochrondria of the different types of cells: A, typical cells lining the residual lumen and a trabeculum of long columnar cells which extend into pars intermedia; B, two typical cells forming the main bulk of pars intermedia; C, three small cells found next to pars nervosa; D, cells from the wall of a colloid-containing vesicle. Neutral formalin-potassium dichromate fixation; acid fuchsin-methyl green stain. X 1000. E, small area from pars intermedia and adjacent pars nervosa showing relation of colloid masses to surrounding tissue. Hematoxatin and eosin. X 265.

shown by Cooper ('19, fig. 4 B) in the California ground-squirrel. Protoplasmic trabeculae appear to project far beyond the deepest nuclei but gradually diminish in size till beyond recognition. Long spindle-shaped cells, sometimes reaching through the entire thickness of pars intermedia, have been observed in several other species (Herring '08). At the surface where the columnar cells become continuous with the flattened cells, transitional forms are found. Each trabeculum is marked by a depres-

sion so that the anterior margin of pars intermedia is scalloped when seen in section (fig. 1).

The cytoplasm, though very scanty in the columnar cells especially, is well provided with mitochondria (fig. 5 A). The nuclei of the columnar cells are long and spindle-shaped and very hyperchromatic.

Another type of cell is found associated with the larger masses of colloid, which appears more or less abundantly. Occasionally a colloid mass is seen which is larger in diameter than the thickness of the entire juxtaneural lobe. Such accumulations as are shown in figure 5 E are more common. The larger masses contain a series of vacuoles around the margin (fig. 5 E). These are most likely the effects of some of the reagents. While the smaller colloid bodies are surrounded by the usual type of cell as if they had accumulated in intercellular spaces, the larger ones are surrounded at least partly by what appears to be a special epithelium. This epithelial wall is usually a single layer of cells but in places may consist of a double layer. An incomplete wall is seen in the largest vesicle in figure 5 E. The cells vary in shape from squamous to columnar. They are much smaller than the majority of the cells in pars intermedia. The cytoplasm is more homogeneous in appearance and, as pointed out by Lewis and Maurer ('20) in the pig, is very poor in mitochondria (fig. 5 D). The nucleus has a dense reticulum containing many large blocks of chromatin. Small masses of colloid may be found either in the cells or between them (fig. 5 E). These colloid cysts are not to be confused with the detached portions of the residual lumen mentioned by Vanderburgh ('17) in the guinea pig.

e. Residual lumen

A distinct residual lumen (hypophyseal cavity) is always present. It frequently contains colloid. While in general its outline is regular, it may be broken up at the margins by a fusion of its walls. As a result of this, small detached acini-like structures with high columnar cells and almost invariably containing colloid may be found between pars intermedia and pars anterior beyond the lateral borders of the main cavity. It is possible that some of the acini occasionally described in pars anterior as having columnar cells and a lumen containing colloid are similarly detached portions of the hypophyseal cavity. In the woodchuck the columnar cells forming the wall of the detached cavities are

identical with those found in groups or trabeculae along the posterior wall of the main cavity; but, unlike the guinea pig's hypophysis (Vanderburgh '17), there are no cilia. When some of these outlying acini are followed in serial sections, they are found to communicate with the main lumen. Others have been completely cut off. As already mentioned, in rare instances the cavity may extend into pars nervosa along with the invading masses of pars intermedia cells. The residual lumen does not extend up along the infundibular stalk. No cilia were ever seen with certainty projecting into the cavity. It is surprisingly free from cellular debris.

f. During hibernation

In comparing the hypophysis as above described, which may be taken as the condition existing in the autumn before hibernation, with those taken from dormant animals, the difference, if any, was so slight that nothing short of careful volumetric analysis could be relied upon. Any unusual feature found during winter sleep could usually also be found in non-hibernating ones. There seemed to be nothing that was characteristic of the hypophysis during dormancy. The hyperchromatic and pycnotic character of the nuclei, described as being typical of the hibernating state, was found only here and there and was just as evident before lethargy. Methylene blue was purposely introduced to give a sharper nuclear stain but neither this nor hematoxylin, to say nothing about the other stains, brought out any difference. Nor was there any apparent difference in the average size of the cells. Limited regions were found in pars anterior of all the animals where the cells were smaller than usual. These areas are so irregular that no general examination warranted any statement as to the relative number of cells involved. The cells of pars anterior in the neighborhood of pars intermedia and the residual lumen invariably are smaller than the average. On the other hand, cells on the outer margin are slightly larger. This was true of all the animals and not merely in those hibernating, as one would infer from Cushing and Goetsch ('15). Judging from the area and number of sections the whole organ did not seem particularly smaller during hibernation, as has been reported, when the body weight was taken into consideration.

g. Post-hibernating period

There was, however, an unmistakable difference in several particulars between the hypophyses taken in the spring, after resumption of activity, and those taken from dormant animals and from animals killed before the onset of winter-sleep. These variations, together with the general similarity between lethargic and pre-lethargic animals, can best be demonstrated by a consideration of the results obtained by the volumetric study carried out. It might be stated here, however, that no evidence of cell division was seen in any case, notwithstanding the fact that such has been seen by Gemelli and by Cushing and Goetsch during the post-hibernating period and that the material here used was fixed instantaneously *in situ* immediately after death. Washing out the blood before perfusing with the fixer is a possible though not very probable explanation of this negative result.

TABLE 1.

Volumetric data on the whole hypophysis and its three principal parts before, during and after hibernation in the woodchuck.

Animal				Whole Hypophysis		Percentage of Whole Hypophysis Formed by		
Number Involved	Number of Each Sex	Rectal Temperature °C.	Av.—Average Mi.—Minimum Ma.—Maximum	Volume cc.	Percentage of Maximum Gross Body Weight	Pars Anterior (Distalis)	Pars Intermedia (Juxta-neuralis)	Pars Nervosa (Processus Infundib.)
BEFORE HIBERNATION								
9	4 Female 5 Male	35 to 38	Av. Mi. Ma.	0.00633 0.00545 0.00750	0.000235 0.000161 0.000280	47.2 40.6 50.7	2.41 0.97 3.84	50.4 45.5 56.3
DURING HIBERNATION								
9	4 Female 5 Male	7 to 16	Av. Mi. Ma.	0.00641 0.00542 0.00741	0.000235 0.000198 0.000291	44.9 34.6 50.6	2.51 1.05 3.71	52.6 45.9 63.2
AFTER HIBERNATION—NOT FED								
9	4 Female 5 Male	34 to 37	Av. Mi. Ma.	0.00865 0.00488 0.01099	0.000322 0.000222 0.000380	43.7 38.4 49.7	2.76 1.60 3.56	53.5 47.0 59.3
AWAKE SEVERAL WEEKS—FED ONE, TWO OR THREE WEEKS								
3	2 Female 1 Male	36 to 38	Av. Mi. Ma.	0.00722 0.00500 0.01027	0.000312 0.000267 0.000353	45.6 37.5 53.7	2.51 1.80 3.21	51.9 44.5 59.2

VOLUME OF THE PRINCIPAL PARTS OF THE HYPOPHYSIS

a. Before Hibernation

The results of the volumetric analysis of the parts of the hypophysis of thirty animals with related data are tabulated in table 1. The volume of the whole hypophysis is merely the sum of the three principal parts which are listed in the last three columns. The average of the nine hypophyses obtained before hibernation was 0.00633 cc. Rather than making an extensive table with individual volumes, the condensed tabulations include only the smallest and the largest organ encountered in addition to the average, in order to indicate the range of individual variation. These limits happen to be very narrow in this group (0.00545 to 0.00750). It must be remembered that these volumes refer to the fixed material and therefore represents only about half of the real volume (Jackson '17). Since the hypophyses of the larger animals are, as a general rule, larger than those of the smaller animals, it is necessary to take into account the size of the animal. This has been done by placing in the next column the percentage of the body which is represented by the organ, assuming that its specific gravity is 1. This averages 0.000235 per cent, but there is an enormous individual variation (0.000161 to 0.000280). Although such marked variations have been noted in other animals (Hatai '13a, Jackson '17, and others) as well as in man, one source of error here is the necessity of taking the gross (and not the net) body weight. From over a hundred woodchucks in which the writer has determined the gastrointestinal contents it may be said that the gross body weight includes anywhere from 1 to 10 per cent of such contents. But this seemed unavoidable because the essential point to determine was to what extent the hypophysis was modified by hibernation and by the restoration of activity, etc., but during this time the body weight is decreasing from lack of food and water till at the time of awakening 25 to 30 per cent has been lost.

The body weight was obtained in the fall before hibernation by weighing the living animal on a spring scale. Those that were kept in captivity for some time were weighed several times before dormancy set in. Each animal was ear-marked with a punch so as to be identified. Although many of the animals were kept under conditions which were almost identical with the normal

habitat (Rasmussen '15), some lost and others gained weight while being fed in the fall before hibernation. Therefore, the maximum body weight obtained while active was used in making the calculations listed in tables 1 and 2. Nearly all the animals weighed between 2000 and 3000 grams.

From the last three columns in table 1 it is seen that the glandular portion (pars anterior and pars intermedia) constitute about half of the organ and pars nervosa the other half. Pars anterior varies from 40.6 to 50.7 per cent, average 47.2 per cent. Pars intermedia represents only 2.41 per cent on the average, but varies enormously (0.97 to 3.84 per cent). As will be shown in table 2, this variation is largely due to a sex difference. The females have a much smaller pars intermedia, but since the number of animals of a particular sex is the same in each of the three principal groups, this does not invalidate seriously a comparison of averages based on both sexes in these groups.

When compared with the only other data which have been found on the proportion of the whole organ formed by the principal components (Jackson '17, on the rat, Björkman '15, on the rabbit), it is found that pars anterior of the woodchuck constitutes about half and pars intermedia only about one-third the proportion that the corresponding parts represent in the hypophysis of the albino rat. On the other hand pars nervosa is more than six times the proportion found in the rat. In the rat, pars intermedia is as large as pars nervosa and each constitutes about 7½ per cent of the whole organ. In the rabbit, the proportions are much like those in the rat in that pars anterior constitutes by far the greatest bulk (66-73 per cent); while pars nervosa represents from 14 to 19 per cent, and pars intermedia 10 to 15 per cent. Numerous comparative data on the size of the hypophysis are given by Livon '09, but these refer only to the organ as a whole.

b. During hibernation

The figures obtained from the nine dormant animals are in every particular essentially like those from animals killed before hibernation. All are well within probable errors when individual variations and the limited number of animals are taken into consideration. If the percentage which the organ formed of the body weight had been calculated from the weight of the animal when killed, the hypophysis would have appeared to be about 25

per cent larger than is characteristic of the pre-hibernating stage, hence the necessity of knowing the original weight before emaciation sets in. It is reasonably certain, therefore, that the hypophysis does not diminish in size during hibernation in the woodchucks here investigated.

c. After hibernation

In comparison with the two preceding groups this third group, which consists of animals that had been awake from several days to several weeks with no food available, shows an increase of fully one-third in the size of the hypophysis. The whole gland varies from 0.000222 to .000380 per cent of the maximum gross body weight, average 0.000322. This agrees with the findings of Gemelli and of Cushing and Goetsch. There is not enough variation from the above two groups in the relative proportion of the lobes to indicate any particular difference in the rate of hypertrophy of the three parts. If anything, pars nervosa has increased slightly more than pars anterior—just the reverse of what one would expect from the supposed decrease in the latter pictured by previous investigators.

The reason for this general hypertrophy has already been suggested earlier in this article where reference was made to increased activity especially in the sex gland during the rutting period and the interrelation of the hypophysis and gonads. The great variation in pars intermedia is again largely due to a sex difference.

Attention should be drawn to the difference in the effects of inanition in this hibernating species of rodent even when active and in the albino rat, a non-hibernating rodent. Jackson ('17) found in the adult that inanition produced generally a relative decrease in pars anterior with evidence of atrophy and degeneration. In all probability animals that regularly hibernate have a degree of resistance to inanition and other conditions such as is not generally found. The storage of an enormous amount of fat and the great reduction in oxidation readily suggest that inanition effects during dormancy would be largely obviated; but it is rather strange that upon waking up and becoming active after one-fourth or more of the body weight has been lost, there are no inanition effects even after three or four weeks deprivation of food and water with rapid loss of body weight.

The last group of three animals, fed one, two or three weeks respectively after having been awake several weeks without food, do not differ essentially from those that had not been fed. It is evident that the hypertrophy of the hypophysis during the rutting season goes on independently of the food factor.

d. Sex differences

The volumetric data on the lobes brought out the fact that there is a fairly constant sex difference. To show this more clearly, all the females were grouped together and an equal number of males so that there were as many males as females from each of the four groups or stages. The results are tabulated in table 2. It appears from this that the male gland is about 13

TABLE 2.

Sex differences in the hypophysis of the woodchuck based on 13 males (average body weight—2638 grams) and 13 females (average body weight—2480 grams). Males 6.4 per cent heavier than the females.

Sex	Whole Gland		Pars Interior		Pars Intermedia		Pars Nervosa	
	Volume cc.	Per cent of Body Weight	Volume cc.	Per cent of Body Weight	Volume cc.	Per cent of Body Weight	Volume cc.	Per cent of Body Weight
Male	.00734	.000278	.00348	.000132	.00022	.0000083	.00365	.000138
Female	.00614	.000248	.00296	.000120	.00014	.0000056	.00303	.000122
	Larger in Male than in Female by 19.5 per cent		Larger in Male than in Female by 16.9 per cent		Larger in Male than in Female by 56.8 per cent		Larger in Male than in Female by 20.4 per cent	

per cent heavier than the female when the 6.4 per cent difference in body weight is taken into account. Similarly each lobe is larger in the male. Pars nervosa follows closely the whole organ but pars anterior is only about 10 per cent larger in the male. It is pars intermedia, however, that is markedly different in the two sexes, being 50 per cent larger in the male than in the female of the same body weight. Of the 13 females only one had a gland near the upper limits and of the males only one had a gland near the lower limit.

In albino rats above 50 grams in weight the females have a larger hypophysis than the males (Hatai '13a). Jackson ('17) finds that this is chiefly, if not entirely, due to a larger pars anterior. His figures on pars intermedia, however, indicate, if anything, that it is slightly larger in the male. Wittek ('13)

found that in cattle the hypophysis is also relatively larger in the female. In the human species (Caselli '00, Lucien '11) the female hypophysis is apparently slightly larger, especially as percentage of body weight and the same seems to be true of the rabbit (Björkman '15).

Pregnancy, which may cause enlargement of the hypophysis (Comte '98, Erdheim and Stumme '09 and others), is no complicating factor in the animals used for this study since the woodchuck does not breed in captivity. All the reproductive organs of these animals were carefully examined and fixed for other studies and no cases of pregnancy were found.

TABLE 3.

Volumetric data on the parenchyma cells of pars anterior and pars intermedia of the hypophysis of the woodchuck before, during and after hibernation. All figures in micra. Same animals in the various groups as in Table 1.

Av.—Average Mi.—Minimum Ma.—Maximum	PARS ANTERIOR				PARS INTERMEDIA			
	WHOLE CELL		NUCLEUS		WHOLE CELL		NUCLEUS	
	Volume	Diameter	Volume	Diameter	Volume	Diameter	Volume	Diameter
BEFORE HIBERNATION								
Av.	854.2	11.8	84.9	5.45	1790.8	15.1	108.5	5.92
Mi.	781.9	11.4	76.0	5.25	1524.5	14.0	103.3	5.82
Ma.	922.8	12.5	88.2	5.52	2047.6	16.0	119.0	6.10
DURING HIBERNATION								
Av.	860.3	11.8	90.7	5.57	1889.9	15.3	108.8	5.92
Mi.	814.5	11.6	83.5	5.42	1349.3	13.0	105.5	5.86
Ma.	1098.1	12.8	100.8	5.77	2563.7	17.4	131.1	6.30
AFTER HIBERNATION—NOT FED								
Av.	847.5	11.7	92.1	5.60	2392.5	16.6	118.8	6.10
Mi.	671.3	10.8	81.2	5.37	1952.5	15.0	106.4	5.88
Ma.	1005.2	12.4	105.1	5.86	2865.0	18.0	132.6	6.33
AWAKE SEVERAL WEEKS—FED ONE, TWO OR THREE WEEKS								
Av.	881.1	11.9	96.0	5.68	1668.4	14.7	111.7	5.97
Mi.	814.5	11.6	94.4	5.65	1504.4	14.2	102.5	5.81
Ma.	915.0	12.0	97.4	5.71	1790.8	15.0	121.1	6.14

SIZE OF CELLS AND NUCLEI IN PARS BUCCALIS

a. Pars anterior

The result of the volumetric study of cells and nuclei of thirty animals are collected in table 3. With reference to pars

anterior before hibernation it is seen that the average cell diameter is 11.8 μ and the average volume is 854.2 cu. μ. The nuclei average 5.45 μ in diameter and 84.9 cu. μ in volume. During hibernation these figures are not decreased, being the same for the cell and slightly larger for the nucleus. Similarly after hibernation and before feeding there is but little change in the size of the whole cell (a decrease, if anything, but too slight to be of any significance), but the nucleus apparently slowly increases. There are so few animals in the last group that the effect of feeding is not established.

The atrophic changes during hibernation described by Gemelli and by Cushing and Goetsch are not supported by these measurements, nor do the cells as a whole seem to get larger after becoming active in the spring.

The inanition effects described by Jackson ('17) in the rat (reduced and vacuolated cytoplasm, hyperchromatism and pycnosis of the nucleus) are not in evidence in the emaciated woodchuck.

b. Pars intermedia

The cells in pars intermedia (excluding the smaller cells, with hyperchromatic nuclei and located in the posterior portion and also excluding the cells lining the residual lumen) are about twice the size of the cells of pars anterior. The nuclei are also

TABLE 4.

Relative number of acidophilic and basophilic cells in pars anterior of the woodchuck hypophysis based on counting from 206 to 284 fields in each of four animals (2 males and 2 females) in each of the three groups. Figures refer to the number of cells per field.

The headings below refer to the averages obtained from individual animals.	Before Hibernation		During Hibernation		After Hibernation	
	Acido.	Baso.	Acido.	Baso.	Acido.	Baso.
Average of all four animals	36.3	4.5	40.6	4.7	46.9	14.7
Minimum	33.8	1.1	38.5	4.0	40.3	12.6
Maximum	39.2	12.7	44.6	4.9	54.4	16.7

larger being nearly 6 μ in diameter as compared with 5.5 μ, the diameter of pars anterior cells. Here again there is no difference between the pre-hibernating period and that of dormancy. The third, or post-hibernating group, shows a perceptible increase in the size of both cells and nuclei. This, however, is not supported by the three fed animals in the last group.

RELATIVE NUMBER OF ACIDOPHILES AND BASOPHILES IN PARS ANTERIOR

a. Before hibernation

To check the assertion that during hibernation there is a loss of the differential staining power of the cells in pars anterior, the average number of acidophiles and basophiles present in a microscopic field was determined in two males and two females from each of the three principal groups. These data, as filed in table 4 show that before hibernation there were 36.3 acidophiles and 4.5 basophiles per field. The basophiles varied between such wide limits (1.1 and 12.7) that the average is not worth much. The mean value was, of course, lower than the average.

b. During hibernation

The figures obtained during hibernation do not vary much from those already given. The range of variation was much more limited in the case of the basophiles, while the acidophiles are slightly more numerous. Dormancy, therefore, produces no striking modification in the number of chromophilic cells which appear as a rule at least as numerous during hibernation as before. One case was found to contain three times as many basophiles before as was ever found during lethargy but the rest had distinctly fewer. The intensity of the differential stain was as great as was generally the case in the preceding group.

c. After hibernation

After waking up a marked increase in the number of basophiles is indicated (14.7 as compared with 4.7 during and 4.5 before hibernation). There appears to be only a slight increase in acidophiles. Since the anterior lobe is a third larger at this time (table 1), the total numerical increase is unquestionable—amounting to about four times in the case of the basophiles. This increase in chromophile cells fully accounts for the enlargement of the pars anterior. The basophiles also stain more strongly with the basic dyes so that they stand out more prominently. The macula is therefore more evident in thin sections and the whole Golgi apparatus—if such it is—is generally larger than at any other time. The increased differential staining properties of the basophiles is fully in accord with all previous observations. It cannot be said that the acidophiles stain more intensely.

Here again the decrease in the specific staining reaction noted by Jackson ('17) in the rat during inanition is not dupli-

cated in starving woodchucks with a loss in body weight from 30 to 40 per cent, in round numbers (Rasmussen and Rasmussen '17, p. 141).

d. Significance of the different types of cells in pars anterior

The many writers that have commented on the significance of the different types of cells in pars anterior (for literature Biedl '16, Schäfer '16, Cooper '19) may be classified into two main groups. Probably a majority (St. Remy, Benda, Caus and Van der Stricht, Herring, Stendell, Pirone, Launois, Thaon and Joris, Sandri, Noronha, Vanderburgh, Cooper and others) favor the view that they are merely different functional stages of the same general type of cell. The basophilic are generally regarded as containing the ripe secretion and the other types as being in earlier stages of the secretory process. The other group (Lothringer, Rogowitsch, Stieda, Flesch, Gemelli, Scoffidi, Thom, Guerrine, Erdheim, Kon, Kraus, Schäfer, Addison, etc.) believe they represent at least two different functional types, there being a strong tendency to favor the derivation of the chromophiles from the chromophobes, but to consider the acidophiles and basophiles as functionally different; but ideas vary greatly.

The almost total lack of intermediate forms, particularly between the acidophiles and basophiles, as judged after staining with a differential stain such as Mallory's acid fuchsin—aniline blue—orange G, does not favor the view that the three kinds of cells are different functional stages of the same cell. In the very active rutting period when the hypophysis enlarges, one would from the first theory expect to see many transitional forms.

The lack of any modification of the general cell picture during profound dormancy in the woodchuck leaves us with no positive suggestion from this source as to the functional significance of any of the constituents of the hypophysis; but the marked response to increased activity shown by the basophilic cells, indicates that this type is more intimately related to processes which are readily influenced by the changed conditions incident to hyperactivity. The susceptibility of the basophiles is also shown by the increase in size, number and vacuolization which they undergo in the albino rat after castration (Addison '17a). Although the acidophiles also are affected by ovariotomy in the human female, Rössle ('14) noted as well a decrease and even

lack of basophiles. Possibly in time the greatly modified basophiles pictured by Addison in the rat would become so necrotic as to be absorbed, thus bringing the above two observations into substantial agreement. According to Lucien ('11) there is a marked increase in the basophilic cells in the aged and Raeder ('20) reports that in the feeble-minded, where the hypophysis is involved more often than any other ductless gland, the most frequent change is a deficiency of the basophilic cells.

Until the appearance of the different cells during specific stages of their activity is more fully known it is hazardous to attempt any elaborate interpretation of the findings here reported.

SUMMARY

1. The hypophysis cerebri of the woodchuck has all the structures generally recognized. The processus infundibuli and the distal portion of the infundibulum are solid. There is a well preserved residual lumen. The whole organ (after fixation and embedding) forms normally 0.000235 per cent of the gross body weight.

2. Pars anterior (distalis) forms a crescentic lobe which constitutes 46 per cent of the entire organ before and during hibernation. It has the usual rich blood supply. Three types of cells are recognized in this lobe: chromophobes, acidophiles and basophiles. The lack of intermediate forms (tinctorially) militates against the theory that these three types are only different functional stages of the same cell.

3. Pars intermedia (juxta-neuralis) represents only 2.46 per cent of the whole gland (average of pre-hibernating and hibernating stages). The great bulk of this structure is composed of the usual large cells. An irregular stratum of smaller cells forms the posterior boundary. The cells next to the residual lumen are greatly modified into squamous and into long spindle-shaped columnar cells. Colloid is frequently abundant—the larger masses being partly or entirely surrounded by a wall of special cells.

4. A sex difference is apparently revealed by the volumetric analysis of the lobes. The male gland averages 13 per cent larger than the female. This difference is equally shared by pars nervosa and pars buccalis (glandularis), but of the two components of the latter pars intermedia is 50 per cent larger while

pars anterior is only 10 per cent larger in the male. However, only 26 animals (13 males and 13 females) are considered.

5. Hibernation produces no change in the weight or histological structure of the hypophysis when compared with the pre-hibernating gland, which is the standard of greatest reliance. The atrophic appearance of pars anterior (suggesting a stage of hypofunction) as previously reported is not confirmed.

6. Immediately after waking up in the spring, during the rutting season, hypertrophy takes place in the hypophysis amounting to 33 per cent in animals kept in captivity. This is distributed proportionately among the three principal parts of the gland. The chief cells and their nuclei in pars intermedia apparently increase slightly in size. While the average volume of the cells in pars anterior shows no variation, the nuclei show a little enlargement. The conspicuous change accompanying the heightened activity is a tripling of the relative number of basophiles and a distinct increase in their staining reaction.

7. It is believed that a failure to compare the hypophysis of the hibernating stage with that of the stage just before the onset of dormancy and the tendency to interpret the post-hibernating conditions as the normal state, are responsible for the idea that winter-sleep in the marmot produces atrophic changes. The return to the pre-hibernating condition evidently occurs late in the summer after the active stage of the sexual cycle has terminated, as is the case with the interstitial cells of the testis and ovary. The limited number of animals involved and the great range of individual variation are also probable sources of error which are to some extent applicable to this study as well.

8. There is a striking difference in the reaction of the woodchuck and of the albino rat (a non-hibernating species) to inanition. While inanition in the rat produces atrophic changes in the hypophysis (Jackson), starvation even in the spring during several weeks of activity and after three months deprivation of food during dormancy, is attended with no such characteristics but rather with hypertrophy of the whole organ and hyperplasia of some of its elements.

I wish to express my appreciation of the valuable assistance rendered by Dr. Sutherland Simpson (Cornell University, Ithaca, N. Y.) in the securing of material and by Dr. C. M. Jackson in connection with the volumetric methods and in the form of many other suggestions. Credit is also due Mr. G. H. Childs for the careful preparation of the illustrations.

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THE CONTROLLING FACTORS IN AMPHIBIAN METAMORPHOSIS: A REVIEW

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(Contributions from the Zoölogical Laboratory of the Museum of Comparative Zoölogy at Harvard College, No. 327, and from the Bermuda Biological Station for Research, No. 124.)

I. In the study of the factors which control the developmental processes in animals, the most fruitful results undoubtedly have been achieved in the investigations upon the metamorphosis of amphibians. The profound changes which are attendant upon the process of metamorphosis occur with great abruptness and are obviously the expression of correspondingly abrupt alterations in the physiological processes within the organisms. The researches on the endocrine organs have demonstrated that these sudden changes are caused by the secretory activity of the ductless glands; in other words, that the hormones of the endocrine glands control, to a very large extent, the changes which come about during metamorphosis.

The literature dealing with the relation of the ductless glands to metamorphosis is extremely varied, and the results have not hitherto been coördinated in a single paper. In addition, many of the conclusions which have been reported conflict with one another. The writer aims, therefore, to present the subject in the space of a few pages, and, as far as possible, to coördinate the material which has appeared in the literature. The historical development of the work on the ductless glands will not be included since it is widely known and may be found by consulting any text-book of physiology.

Among the ductless glands which function in promoting the developmental processes in amphibians, the most important is the thyroid. This fact was first disclosed when tadpoles were fed upon the desiccated gland.

II. *Thyroid feeding:* Gudernatsch, assuming that during the metamorphosis of amphibians the metabolic rate was abnormally high, concluded that if a substance could be found which would increase the metabolism of the larvae, the speed of metamorphosis would be greatly accelerated. Pragmatically to prove such a contention he undertook a series of feeding experiments in which he attempted to raise the metabolic rate of some young

tadpoles. The work which previously had been done on the endocrine organs had firmly established the fact that certain of the internal secretions effect a high metabolic rate in mammals. This prompted Gudernatsch to employ the extract of several of the ductless glands in his feeding experiments. The results were striking; hardly, however, to be interpreted as the result of a mere increase in the metabolic rate, but rather to an acceleration of the developmental processes themselves. Growth was arrested immediately the extract was administered; particularly was this true in the case of the thyroid, but the developmental processes proceeded so rapidly that within less than a month a mature frog had resulted, which appeared to be normal in every respect save that it was ridiculously small. Thus, though the metabolism may have been greatly stimulated, it did not cause a more rapid growth (that is an increase in size), but was directed to the hastening of development. The initial assumption of Gudernatsch ('12 and '14) that a stimulant of larval metabolism should cause a precocious metamorphosis was thereby justified; the hindering of growth was simply a result which had not been foreseen. The work was immediately confirmed by numerous observers both in this country and in England. Hoskins ('16) of Minnesota showed, not only that metamorphosis was accelerated, but that the thyroid feeding caused also a comparative enlargement of many of the internal organs. Herring ('17) proved that a similar phenomenon occurred when white rats were fed upon thyroid. In short, Gudenatsch's discovery raised a host of interesting problems, the solutions of which are at the present time just beginning to be reached.

The first questions which naturally arose were: Does the thyroid gland in these larval forms bring about metamorphosis? If so, how? What forces does it set into motion? Is it assisted in its work by the other ductless glands? What relation does the thyroid bear to the nervous system? The thyroid gland was known to contain iodin. What, then, is the relation of iodin to the thyroid and to metamorphosis? These are only a few of the more important questions which were immediately raised after the discovery had been made known.

III. *Thyroidectomy:* The first question—does the thyroid gland cause metamorphosis—might reasonably be answered if it could be shown that thyroidectomy prevented metamorphosis.

The operation involved in removing the anlage of the thyroid gland from young larvae is uncommonly difficult. It was accomplished simultaneously, however, by two investigators who worked independently. To quote Hoskins and Hoskins ('19):

> "The first operations were performed by one of us in April, 1916, and in the spring of 1917 and 1918 the experiments were repeated. We learned in November, 1916, that Doctor Allen [See Allen, '18] of the University of Kansas, had performed similar experiments with R. pipiens at about the time when our first were made."

The results of the two experiments accord with each other entirely. They both show that metamorphosis cannot take place in the absence of thyroid gland. The intestine retains its larval characteristics and the development of the brain is almost completely stopped. As to sexual maturity, both authors agree that the development of the gonads is in no way affected by thyroidectomy (Allen '17b). In other words, the hormone which provokes the frog partially to metamorphose has no influence upon sexual growth. Hoskins and Hoskins ('19) note further that the lungs seem also to continue their normal development. The liver, thymus,[1] spleen and kidney are arrested in their growth and continue to retain their larval form. In addition to these features, the larvae grow rapidly and attain sizes which sometimes are absurdly large. In the Hoskins' experiments, one grew to a length of 72 mm. while control specimens averaged between 40 and 45 mm. Thyroidless larvae have been kept over a period of more than two years without completion of metamorphosis.

The earliest apparent differences between thyroidectomized and control larvae are in the skeletal elements. It would seem, inasmuch as the legs fail to develop normally, that the calcium metabolism must be interfered with by the thyroid removal. Terry ('18) describes the general processes of calcification and ossification as progressing much more slowly in the operated tadpoles.[2] Buds of legs appear, it is true, but their failure further to develop is caused by the failure on the part of the skeletal part to push into the buds. Nevertheless, it seems to me highly questionable that the thyroid directly controls calcium metabolism. The pituitary has been demonstrated (p. 86 below) to

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[1] That the thymus should fail to undergo atrophy as a result of thyroid removal does not indicate a close connection between the two glands, but simply that the thymus along with many other organs fails to lose its larval form. This fact Rogers ('18) fails to observe.

[2] Hofmeister ('94) also noted that thyroidectomy was followed by an abnormal growth of bones.

have a direct connection with the growth of bones, and it appears more probable that the changes which occur in the pituitary after thyroidectomy themselves in turn affect ossification. In this light, the thyroid would control calcification only in so far as it had control over the hypophysis. It has also been suggested that the hypertrophy of the hypophysis following thyroid extirpation may be responsible for the acceleration in growth rate of the thyroidless tadpoles (Hoskins and Hoskins, p. 18).

In view of the fact that the lungs continue their normal development, it was of interest to see whether the thyroidless larvae would live out of water. On being put in a moist chamber they continued to live for two days, but owing to the fact that food could not be obtained as under normal circumstances, death threatened from inanition. The Hoskins ('19) tried also to force metamorphosis by putting the larvae in a moist chamber on a bed of wet Spirogyra, where they were kept for two days. Though there was a slight diminution in the tail volume and length, no positive results were obtained.

At this point an observation of Allen's ('18, p. 508) is of interest. He found that, though metamorphosis be arrested by thyroidectomy for as long as four months, yet if the tadpoles are fed upon desiccated thyroid the process of metamorphosis is resumed, and normal frogs result. This is of singular interest since it shows that the thyroid hormone is capable of promoting metamorphosis in the absence of the gland itself, that the active principle which produces the changes occurring in metamorphosis is a definite chemical substance, and not one which requires the living cell to synthesize it at the moment it is needed. It would seem to indicate further that the thyroid gland functions rather to store certain chemical substances taken in as food than to manufacture them.

Undoubtedly the most remarkable result of the investigations on thyroidectomy is the effect—or, better, the lack of it—which the operation has upon the *germ* cells. Apparently they continue their development totally unaffected. It has been shown by Swingle ('18b) that inanition may hinder greatly the development of germ cells. The same investigator ('18a) declares that feeding with thyroid extract, though greatly accelerating development, in no way hastens the growth of the gonads. Also Allen ('18) and other observers have emphasized the fact that thy-

roidectomy does not delay in the slightest the development of the testes and ovaries. In other words, substances which hasten the proliferation of the soma cells do not materially affect the germ cells. It is interesting to speculate concerning the bearing which these facts may have upon Weismann's hypothesis concerning the independence of germ and soma. Certainly a very marked degree of independence is here manifested beteen the two types of tissue. Whether a complete independence exists, is very difficult to determine with accuracy. Spermatozoa actually were seen in both Allen's and the Hoskins' larvae. The growth of oöcytes was, on the other hand, definitely slower, the largest which were obtained being about 300 micra in diameter. There seemed to be no definite correlation between the development of the oöcytes and the bodily growth and in none of the experiments were sufficiently mature eggs formed to make larval reproduction possible.[3] If larval reproduction can be effected under laboratory conditions, the outcome will be of singular interest to the student of Weismannism.

Superficially, the results recorded above may seem to conflict with the conclusions reached by Hofmeister, Jeandelize and Eiselsberg, who state that thyroid removal in the higher animals has a detrimental effect upon the gonads. It must be recalled that their experiments were performed, for the most part, upon adult animals. In such cases, the effect seems rather to disturb the physiological equilibrium than to prevent the growth of the gonads. In this connection, a view expressed by Max Kollmann ('19) is of interest. He believes that the thyroid gland favors the permanence of certain secondary sexual characters, but that it does not bring about their growth. In other words, having once reached sexual maturity, the thyroid is needed to maintain the physiological balance. That this is the case also seems evident from a recent work of Giacobini ('19), who has shown that sterility in women is frequently caused by a deficiency of the thyroid.[4]

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[3]Duméril ('67) has reported larval reproduction in amblystoma tigrinum found near Lakes Xochimilco and Chalco (eight miles from Mexico City)—a region which is practically free from any taces of iodin (Gadow, '08). De Filippi ('61) also found Triton larvae with mature sex organs in the Formazza valley, near Andermatten.

[4]He states also that thyroid injections relieve incipient symptoms of sterility.

Unfortunately, no attempts have been made as yet to force thyroidectomized larvae which have metamorphosed on a thyroid diet, to reproduce.

The theories of Uhlenhuth regarding the effect of thyroidectomy will be discussed below.

IV. *Iodin and the thyroid:* The relation which the halogen atom, iodin, bears to the thyroid, and more especially to the phenomena of amphibian development, has long been disputed and is at the present time still an unsettled question. As early as 1820 iodin was used in treating diseases of the thyroid, but it was not until 1895 that Baumann actually demonstrated the existence of this substance in the follicles of the gland, and proved that it was compounded with a protein. As to the powers of the thyroid secretion there are those who maintain that its activity is determined by its iodin content, and another group who believe that the amount of iodin which the thyroid contains is entirely a secondary factor, and that its power to stimulate metabolic processes depends upon the protein molecule with which the iodin is associated.

The chief cause of the disagreement lies in the interpretation of the results obtained from amphibian experimentation. Let us examine first the evidence of those who hold that iodin is the active element.

Marine and Williams ('08) observed that when thyroglobulin rich in iodin was fed to dogs they lost more weight than when the preparation contained a smaller percentage of iodin. Hunt ('07) and Hunt and Seidell ('08) also concluded that the activity of the thyroid depended upon its iodin content. By testing the various substances obtained by alkaline hydrolysis on metamorphosing tadpoles, Marine and Rogoff ('16) reached the same conclusion. In the same year, Oswald expressed a view which entirely accords those just noted. G. E. Smith ('17) also has shown that birth mortality in pigs in regions where the "hairless pig malady" occurs is greatly lessened if the sow is fed upon iodin during gestation.

The most important results, however, are those of Swingle ('19a and b). He found, in the first place, that if tadpoles are fed upon a mixture of one part iodin and one hundred parts flour, their metamorphosis is greatly accelerated, identically as it is by feeding with thyroid extract. KI has a similar effect but

it acts much more slowly, while iodoform is excessively toxic. With the mixture of iodin and flour, Swingle found that growth was stopped almost immediately, but that complete metamorphosis had resulted in less than a month. The writer repeated this portion of Swingle's work while at Bermuda Biological Station (1919) and attained results which were practically identical with those of Swingle. The iodin feeding was conducted on Bufo agua larvae which averaged about 10 mm. in length. Seven days after the first administration, hind limb buds were very clearly in evidence. The fore-limb buds appeared four days later. At the end of twelve days the hind limbs were 3 to 4 mm. in length and atrophy of the tail had set in.[5]

Swingle carried the work still further and found that thyroidectomized larvae would immediately metamorphose if put upon a thyroid diet. This result is undoubtedly far-reaching in its importance. The two most interesting deductions, to use Swingle's own words ('19a, p. 413), are as follows:

"If animals without the vestige of a thyroid gland are stimulated to complete metamorphosis in an abnormally short time by iodin, it would appear that iodin functions within the organism as a hormone itself, and that the gland functions chiefly for storage purposes. The evidence from the thyroidectomized larvae indicates that the animal body is capable of utilizing iodin directly without the intermediation of the gland."

As an evidence for the theory that the thyroid functions to store iodin for future use, Swingle offers the fact that the glands of iodin-fed larvae are considerably larger than those of the controls, and a histological examination revealed the fact that the colloidal content of the follicles was greatly increased.

The unavoidable conclusion is that, as far as amphibian metamorphosis is concerned, iodin is certainly the activating substance which effects the changes. It would be a stretch of language, however, to say that iodin causes metamorphosis; more accurately, it should be stated that metamorphosis cannot go to completion in the absence of iodin. The processes of development are set in motion by the fertilization of the egg, and the end and aim of the developmental process is the production of a mature frog. The larval stage is reached and all of the potentials

[5]Mr. Leland C. Wyman of the Harvard laboratories is now making a thorough histological examination of the thyroids from the tadpoles used in these experiments.

of an adult frog lie within the cells of the animal, but to complete its development, a call is made upon the environment for iodin. It should be emphasized that the larva has to reach a very definite stage in life history before it can utilize iodin. If administered before a length of approximately 10 mm. is reached, it serves only to kill. The point that must be made clear is that iodin does not cause metamorphosis but simply acts like a lubricant in assisting the developmental potentials residing within the larva.

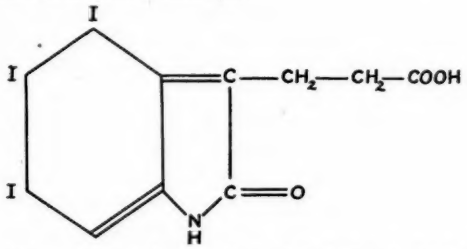
Let us now consider the experiments of those who deny the correlation between iodin and thyroid activity.

Working in the amphibian field, the only two authors whose researches seem to cast doubt upon the functional activity of iodin are Graham ('16) and Abelin ('17). By feeding fractionated parts of the thyroid extract they have gained evidence that some fractions which are really low in iodin content are exceptionally active in promoting metamorphosis. The evidence which they present, while interesting, is by no means conclusive, and particularly must it be accepted with caution after the positive results which Swingle has set before us. There is, however, a series of chemical investigations which demand the most careful consideration.

E. C. Kendall ('18, '19a and b) of the Mayo Clinic at Rochester, Minnesota, after eight years' work, in which he used some two tons of thyroid glands, finally succeeded in isolating and analyzing the active principle of the thyroid gland, and has called it "thyroxin."

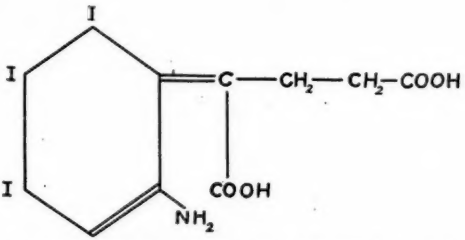
Attacking the problem, as he has, from the chemist's viewpoint, and experimenting liberally upon human subjects, he has reached the conclusion that the iodin content, for man at least, does not give to the active principle of the thyroid its powers to stimulate metabolism. The formulae which Kendall believes to represent the structure of the active principle are two in number: one an active form and the other an inactive substance which exists when the hormone is being held in reserve. The active constituent has as its structural base an indole group possessing three substituted iodin atoms on the benzene ring, and an oxygen

and a propionic acid radical attached to the imino group. Structurally it is represented as follows:



and bears the technical designation of 4, 5, 6 triiodo 4, 5, 6 trihydro 2 oxyinodolepropionic acid; the shortened form being thyroxin.

In an alkaline solution, the NH and CO groups of the imino ring undergo hydrolysis, which results in the opening of the ring and the formation of NH_2 and COOH. This change converts the functioning thyroxin into its inactive form, shown in the next formula:



Both the extract and the synthesized thyroxin act in the same way when put into an alkaline medium; when the solution is made acid, however, the ring closes and the substance again becomes active. It is Dr. Kendall's belief that in the body the conversion from the inactive to the active thyroxin is effected by the action of the amino acids. It has also been suggested that CO_2 may also aid in bringing about this change.

On account of the peculiar action of the imino group in the presence of acids and bases, Dr. Kendall has been led to the belief that the imino side-chain—not the iodin atoms—are responsible for the physiological activity of the substance. He has also furnished experimental evidence to uphold this contention.

One third of one mgm. of thyroxin will increase the metabolic rate of an individual weighing 150 pounds one per cent. The open-ring formula, which contains just as many iodin atoms, increases only in very slight measure the metabolic rate. Hence it seemed reasonable to conclude that it is the closure of the ring which causes its activity.

Those who are skeptical of Kendall's stand have made the suggestion that thyroxin ought still to act if the iodins were replaced by bromine atoms. Swingle ('19c), while not disproving this suggestion, immediately fed some tadpoles upon bromine and found that it in no way stimulated metamorphosis,[6] but was, on the contrary, highly toxic.

Kendall thereupon performed some tadpole-feeding experiments himself and found that both the open-ringed and the closed-ringed thyroxin stimulated metamorphosis in exactly the same way. From these results he arrived at the following conclusions:

"Thyroxin, therefore, appears to have two separate and distinct functions: The effect upon the metabolic rate which is brought about by the CO-NH groups within the molecule; and the physiological changes involved in the metamorphosis of the tadpole brought about by the iodin contained is not specific to thyroxin, but can be obtained by a large number of other iodin compounds and by elemental iodin itself, and appears to be inherent within the iodin atom. But the unique effect of thyroxin on the metabolic rate is due to the specific chemical structure of the molecule and this is not shared with any other substance so far known" ('19b, pp. 136-137).

The view thus expressed seems to be reasonable, and, if accepted, it effects a successful explanation of the divergent views which have heretofore existed concerning the importance of iodin.

Before concluding the consideration of the thyroid and metamorphosis a word must be said regarding the theories which Uhlenhuth ('19d) has recently advanced. According to this investigator there are two substances which incite metamorphosis; one, the iodin, which causes morphological changes such as the atrophy of the tail and the loss of the gills; the other an "excretor substance," a protein, which is produced by growth and which excites the thyroid gland to functional activity. The time of production of this hypothetical excretor substance determines when a larva shall metamorphose. He adds further that the thyroid secretion which is made active by this excretor sub-

[6] It is interesting to note, however, that prolonged inhalation of bromine fumes produces profound changes in the thyroid (Pellegrin, '17).

stance is responsible for growth. It might be noted here that inasmuch as tadpoles which are fed upon iodin do not grow, one could say that it was due to an absence of the "excretor substance." Such hypotheses as these are really of great interest, but until they are backed by experimental proof, they are of little scientific value.

In a later paper, Uhlenhuth ('19e) groups the changes which occur during metamorphosis under four main headings and then attempts to show that the changes in any group can be made to go on independently of the others. He uses the sex organs to illustrate his point. As was shown above, their development can go on independently of the other phenomena of Anuran development. That the other changes—gill reduction, leg growth and the enlargement of the tongue—can go on independently of one another lacks experimental proof.

V. *The other endocrine glands.* From the consideration of the thyroid it is evident that this gland controls the development of a large number of the internal organs; however, it exerts practically no influence over the growth of bones and has little control over the development of the germ cells. Let us, therefore, examine the other endocrine glands and find to what extent they control these processes.

The desiccated substance of the pineal organ has been shown by recent workers to be a powerful metabolic stimulant. McCord and Allen ('17) find that in a dilution of 1 to 100,000 it produces a complete retraction of melanophores of amblystoma larvae. But of much greater importance is the inhibitory effect which the pineal organ appears to have upon the growth of the germ cells. Foà ('12) reports upon an interesting work in which he removed the pineal from roosters, and found that the operation was followed by a marked hyperthrophy of the testes as well as of the crest. The work of Foà has been paralleled recently by some experiments on guinea-pigs. Horrax ('16) studying some eighty cases of successful pinealectomy in guinea pigs and rats, finds the operation had no effect upon body weight, but that it accelerated greatly the development of the testis. This was confirmed both by the early date at which breeding commenced and by histological examination. The results in the female were not conclusive. The work of Horrax needs confirmation. If it can be shown conclusively that the pineal gland exerts a definite

inhibitory influence upon sexual development, it is placed beyond a doubt among the endocrine organs. Whether these observations are applicable in explaining phenomenon of sexual development in amphibians, has never been determined, but it would indeed be of great interest to find whether the maturation of the germ cells would be accelerated in the event of pinealectomy.

As for the parathyroid glands, there is every indication that they are isolated both functionally and anatomically from the other endocrine glands, and probably perform no function in the promotion of metamorphosis. Kamo ('17) reports that the removal of the thyroid produces no effect on the parathyroids; Allen ('19b), however, believes that a slight hypertrophy results. The most interesting function of the parathyroids, however, lies in their power to prevent tetanus.

It has been observed by several, during the last few years, that thymus extract causes violent convulsions when fed to certain amblystoma larvae. The effect was first noted by Lenhart ('15). This peculiar action of the thymus has led to an uncommonly interesting piece of theoretical work by Uhlenhuth. In the first place, he interprets the violent convulsions following thymus feeding as tetanus. He observed further—and it is upon this observation that the validity of his whole theory rests—that the two species of amblystoma which became tetanous when fed upon thymus are species which do not possess the parathyroids until a later stage. He states also that the larvae which have their parathyroids developed do not become tetanous when fed upon thymus (see Uhlenhuth, '18). On a basis of these observations, Uhlenhuth ('19c) concludes that the thymus secretes a tetany-producing substances which is normally neutralized by the parathyroids.

The hypothesis of physiological antagonism which Uhlenhuth has thus set before us is most unusual and requires, therefore, our careful consideration. In the first place, the theory requires corroboration. At present there seem to be open at least three main channels by which further evidence for or against his theory can be secured.

(1) Probably the most vulnerable spot lies in his statement that amblystoma *opacum* and *maculatum* do not possesses parathyroids in the early stages. If it can be shown conclusively that this statement is true, the theory will be put upon a very substantial foundation. (2) Noël Paton and his co-workers ('17) have shown that the salts of guanidine and methyl-guanidine produce all the symptoms of tetany and that the salts of guanidine increase in parathyroidectomized animals. In the light of Uhlenhuth's theory the thymus would probably effect the increase in the salts of guanidine. Hence, if it could be demonstrated that the thymus secretes guanidine, the theory would be well substantiated. (3) A further method for demonstrating the efficacy of Uhlenhuth's theory lies in finding whether an injection of desiccated parathyroids ameliorates in any way the symptoms of tetany (parathyreopriva). Honeyman ('19) working under the direction of Noël Paton, has already attempted to disprove the contention of Uhlenhuth. He removed both the thymus and the parathyroid glands simultaneously from a guinea pig and tetanus ensued in exactly the same manner as it does when the parathyroids are removed. The contrary evidence which he gives is by no means conclusive. The chief objection is that the work was done upon a very much higher animal, and one from which, as a matter of fact, according to Park, the thymus can not be completely removed: It was done, besides, upon a matured animal, while Uhlenhuth's experiments were performed on species which were in their larval stage.

The thymus gland, aside from having little influence upon metamorphosis in amphibians, is probably not an endocrine organ. The investigations of Dustin ('13), Hoskins ('18), and Badertscher ('20) have shown that its most important function is probably in hematopoiesis. The results of thymus feeding

are contradictory. Swingle ('17) reports that it has no effect upon the rate of metamorphosis, and Hoskins ('16) states that it has no constant effect; Gudernatsch ('17), on the other hand, has had positive results in his thymus feeding experiments. Recently, Allen ('20a) has reported evidence that the extirpation of the thymus produces no effect upon the rate of metamorphosis. Uhlenhuth ('19b) has come forward with a theory which aims to account for discrepancies in the results. Put in form of a syllogism the theory would be stated as follows: 1. The thyroid gland causes metamorphosis. 2. In normal food there are certain substances which incite the thyroid gland to secretory activity. 3. In that the thymus as food does not possess substances which incite the thyroid, thymus feeding has an inhibitory effect upon metamorphosis. In the light of his experimental evidence, the theory seems reasonably sound. He fed one set of tadpoles upon thymus, taking pains to prevent any other food substances from getting into the water, and found that the effect was definitely inhibitory. To another group he fed thymus, but permitted other food substances to be contained in the water. This group metamorphosed normally.

Excluding the thyroid, the anterior lobe of the pituitary undoubtedly is the most important of the ductless glands concerned in amphibian metamorphosis. The fact that the hypophysis is associated with acromegaly at once suggests that the gland may control the growth of bones, and the investigations of Erausquin ('17) show that such is the case. It is widely agreed, moreover, that hypophysectomy inhibits growth. The very striking work of Aschner ('12, p. 68) on dogs is an interesting example. From one of two brother puppies the pituitary was extirpated. After six months, the normal pup was very nearly three times the size of its brother. In the amphibian field we have more recently the results of Allen ('17a and '19b) and P. E. Smith ('16a, b and '18) which briefly are as follows: If young larvae have their pituitaries removed, there follows a general retardation of growth, incomplete metamorphosis, a complete retraction of the pigment cells (8 days after extirpation, Allen), failure of legs to develop, and lastly a very marked effect upon the thyroid. The results of feeding pituitary, on the other hand, are somewhat contradictory. Hoskins ('16) believes that it has little or no effect upon growing tadpoles. Smith ('18), however,

reports a marked increase in growth rate both of normal larvae and those from which the pituitaries have been removed. Kojima ('17) shows that feeding of the extract to normal larvae causes a marked hypertrophy of the pituitary gland itself.

It has been believed for some time that the gonads and the pituitary bear an intimate relationship one to the other. According to Noël Paton ('13, p. 186) castration causes marked changes in the anterior lobe of the hypophysis. Addison ('17) has recently made the interesting observation that castration in the Albino rat is followed by a marked increase in the number of basophilic cells in the hypophysis. He believes that the interstitial cells of the testis and the basophils in the anterior lobe are intimately connected and it is his opinion that the latter control the former. In 1916 Goetsch stated that the extract from the anterior lobe when fed to tadpoles greatly accelerates their sexual development. Finding that the extirpation of the anterior lobe causes no change in the testis of amphibians, Allen ('17a) objects strenuously to Goetsch's conclusions. On such a basis it seems to me that the objections are wholly unjustified.

The results of feeding the extract of the anterior lobe of the hypophysis to thyroidectomized larvae are also of great interest. Larson ('19) for instance, has fed the anterior lobe of the hypophysis to thyroidectomized rats, and finds that it has a "beneficial" effect upon their growth. Whether the tethelin (extract of the anterior lobe) takes the place of the thyroid hormone or whether it simply stimulates the metabolic rate was not decided. The experiments of Hoskins and Hoskins ('20) also show interesting results. They find that thyroidectomized Rana sylvatica larvae will almost completely metamorphose when fed upon tethelin. They conclude that the extract acts as a stimulant to the normal metabolic rate.

DISCUSSION

Granting the fundamental principle of the embryologist that "ontogeny tends to repeat phylogeny," a very suggestive deduction is at once forthcoming from the work which has just been discussed. The fact that amphibians in their life history change from water-breathing to land animals makes it evident that land amphibians are descended phylogenetically from the fish. If, therefore, iodin prompts an amphibian to undergo this change

from a water to a land animal what can be said of the factors which control the embryological development of higher animals during the corresponding ontogenetic stages, during the disappearance, for instance, of gill slits from the mammalian foetus? Since iodin causes the atrophy of the gills and other phenomena associated with metamorphosis, according to the principle just enunciated it should likewise effect corresponding changes in the ontogenetic development of higher animals. What evidence can be offered in support of such a deduction?

Dr. C. R. Stockard in his lectures at Wood's Hole during the summer of 1920 expressed his firm conviction that iodin is one of the most important factors which controls the embryological development of mammals. As the result of his experimental work has not as yet been published, one cannot pass judgment upon his conclusions. However, a series of experiments reported by Ukita ('19) tend strongly to support Stockard's stand. This writer has shown that if the thyroid of a pregnant rabbit is removed on the tenth day of gestation, the date of birth of the offspring is postponed from 60 to 70 days, and that the young when born are weak, and are possessed of thyroids which have undergone marked hypertrophy.

Such results as these give to the invesetigations of amphibian metamorphosis an intensely practical aspect, and indicate, in addition, that endocrinology as a science will be concerned in the future not alone with the physiology of mature indviduals, but also with embryological development.

SUMMARY

1. The metamorphosis of amphibians cannot take place in the absence of the thyroid hormone; feeding desiccated thyroid to growing tadpoles greatly accelerates their rate of metamorphosis. Thyroidectomy interferes with bone growth and causes the liver, intestine, thymus, brain, kidney, and spleen to retain their larval state. The gonads and lungs develop normally in the absence of the thyroid. A larva in which the metamorphosis has been arrested by the extirpation of the thyroid will metamorphose normally if fed upon thyroid extract. The thyroid lends permanence to the secondary sexual characteristic rather than causes their growth.

2. The metamorphosis of normal frog larvae is greatly hastened by feeding with organic iodin. Thyroidless tadpoles can be made to metamorphose by iodin feeding.

The structural formula for the active principle of the thyroid has been worked out, and the substance is called thyroxin.

3. The organic extract of the pineal gland accelerates metabolic processes. From the work of Foà and Horrax, it would seem that the pineal hormone inhibits the growth of the testis.

4. Uhlenhuth's theory that the parathyroids in amphibians neutralize a tetanus-producing secretion from the thymus needs further proof.

5. The thymus is primarily a lymphopoiëtic organ. Desiccated thymus does not affect metamorphosis save as it hinders it, when used in excess as food. There is no demonstrated influence which the thymus exerts over sexual development. The thymus is probably not an endocrine gland.

6. The cells of the pituitary are closely related functionally to the interstitial cells of the testis; the anterior lobe probably stimulates sexual development. It also accelerates growth, as feeding experiments with tadpoles show. Further, it assists in bone ossification.

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THE SYMPATHETIC NERVOUS SYSTEM IN DISEASE, by W. Langdon Brown. Published by the Joint Committee of Henry Frowde, Hodder and Stoughton, Ltd., 17 Warwick Square, London, E. C. 4. 10/6 net, 161 p.

This small book of 161 pages deals with a subject the importance of which is just beginning to dawn on the medical profession. The book is based on the Croonian Lectures delivered before the Royal College of Physicians of London in 1918. It seems especially fitting that this important subject should have been emphasized by being discussed before this able body of physicians.

The book is of great interest to students of endocrinology because it points out so clearly relationships which exist between the vegetative nervous system and the endocrine glands. The discussion, however, is confined almost entirely to the sympathetic division of the vegetative system.

The book consists of seven brief chapters in which the anatomy and physiology of the sympathetic nervous system; the sympathetic system in its relation to the endocrine glands, to the digestive and circulatory systems; vagatonia; and general response of the sympathetic systems are discussed. This book helps the clinician in interpreting in terms of physiology many of the symptoms which are commonly met in the every day practice of medicine.

The relationship of the sympathetic nervous system to the endocrine glands is well shown in the following quotation: "Designed as an intensive preparation for action or defense, the sympathetic response may be so dissociated, perverted, or prolonged as to produce through the thyroid gland Graves' disease with its danger to life, through the pituitary body, diabetes insipidus with its attendant discomforts, through the pancreas and other endocrine glands, excessive mobilization of the blood-sugar, which is the first stage of the metabolic disorder that culminates in diabetes; it may disorganize digestion by exciting spasm and atony in stomach and bowels, and inhibiting the secretion of digestive juices; it may keep blood pressure at a level which is inappropriate for the task of the heart and the arteries. These effects are not necessarily distinct—thus, intestinal stasis from sympathetic inhibition causes poisons of putrefactive origin to be absorbed, which in their turn lead to vasoconstriction, and hence an unduly raised blood-pressure."

The relation of the sympathetic stimulation and glycosuria as he sums it up is of especial interest. The author states that underaction of the pancreas and over action of the adrenals, thyroid and pituitary can all lead to glycosuria and that the loss of sugar balance can be produced through the sympathetics in the following way:

"(1) Sympathetic stimulation increases blood-sugar as a defensive measure. (2) Sympathetic stimulation causes increased secretion of adrenals, thyroid, and pituitary. (3) Vagus stimulation excites secretion of the pancreas, and on the generalization of the opposing actions of the parasympathetic and sympathetic it would appear probable that sympathetic stimulation inhibits the secretion of the pancreas; the antagonism between its internal and external secretions does not mean an antagonistic nervous supply; it means a diversion of nervous energy from one channel to another. (4) The general effect of sympathetic stimulation is katabolic, and mobilization of blood-sugar is a preparation for katabolic action. (5) Therefore the sympathetic both by increasing the secretion of glands which diminish carbohydrate tolerance and by inhibiting the gland which increases carbohydrate tolerance, would raise the blood-sugar above the leak-point, and glycosuria would result."

Such data emphasize strongly the interdependence of the vegetative nervous system and the endocrine glands, and show that endocrinology and visceral neurology cannot profitably be treated independently.—F. M. P.

NEUVAS ORIENTACIONES SOBRE LA DIABETES INSIPIDA. By Gregario Marañón, Madrid, 1920.

Starting from the theory of Schäfer, in which a diuretic action is attributed to hypophyseal extracts, the author oriented his own investigations on the supposition that diabetes insipidus is due to an excess of the hypophyseal hormone, that is to say, to a hyperfunctioning of the hypophysis. The results of his studies have given rise to the contrary idea, since he has succeeded in demonstrating that in a large number of cases there are encountered symptoms which point to a hypofunctional disturbance of the hypophysis. This conception is confirmed at autopsy by the finding of lesions which are the effective cause of this essential polyuria. The opinion is strengthened by the specific corrective influence of injections of hypophyseal extracts on the disorder and the action of these preparations in the normal organism.

Marañón concludes that diabetes insipidus is a disease produced by an insufficiency or lack of an internal secretion of the pars intermedia or pars posterior of the hypophysis cerebri, a secretion which normally regulates and moderates diuresis by acting on the renal cells through mediation of a neuro-endocrine complex, or indeed by causing vaso-dilatation of the arteries of the kidney simultaneously with a general modification of the circulatory apparatus.

In concise and suggestive terms, with much erudition Marañón presents the etiology, symptomatology, course, prognosis and

treatment of diabetes insipidus, making of this monograph a work full of interest.—I. O.

THE MORPHOLOGY AND EVOLUTIONAL SIGNIFICANCE OF THE PINEAL BODY, PART I. By Frederick Tilney and Luther F. Warren, Philadelphia, 1919, The Wistar Institute of Anatomy and Biology. The American Anatomical Memoirs.

This monograph represents part I of an extensive study of the pineal body which the authors have undertaken to put out in three parts. Parts two and three are promised to include the physiology, pathology and clinical aspects of the epiphysis.

The authors first take up a general review of the literature concerned with the pineal body from the historical standpoint. This is followed by a very exhaustive review of the comparative morphology, embryology, anatomy and histology of the pineal going from the cyclostomes to the mammals. Following this review there is a discussion of the significance of the pineal region based upon phylogenetic consideration as well as upon histological study.

The summary and conclusions are as follows:

I. The pineal region is preponderatingly glandiferous in its derivatives. The morphogenetic impulse imparted by such a gland-forming area could not fail to have a profound influence upon one of its constituents, the epiphysis.

II. a. The pineal body cannot be a vestige from the evidence based upon its gross morphology, for the following reasons: 1. The phyletic constancy of the epiphysis in the vertebrate phylum; 2. Its variations and morphologic specializations; 3. Its relatively greater phyletic constancy with reference to other structures in the pineal region; 4. The gross evidence of its progressive specialization in ophidians, birds, and mammals; 5. The increase in the epiphyso-cerebral index, from the earliest stages to the latest periods of life in man; 6. The resistance to the encroachment of a prominent neomorph in the mammalian brain, that is, the corpus callosum, which has produced such marked alterations in the other constituents of the diencephalic roof-plate.

b. The pineal gland cannot be considered a vestige in the light of the histological evidence, since the tendency toward specialization is definitely in the interest of glandular formation in ophidians, chelonians, birds, and mammals. Ontogenetically, in two forms at least, in Felis domestica and man, the development of the pineal body follows the general lines of glandular differentiation. The pineal body is, therefore, a glandular structure and as such, is necessary in some way to metabolism.

III. The histology of the organ gives clear evidence that the epiphyseal complex of vertebrates possesses a pluripotentiality the fundamental inherent tendency of which is in the interest of glandular differentiation, but in a few instances, as in cyclostomes, amphibia, and in primitive reptiles, the pineal organ may become further differentiated in the interest of a highly specialized sensory mechanism which has, or has had, visual function. As a gland, it may in some cases, contribute its secretion to the cerebrospinal fluid, but in the higher vertebrates, as in ophidians, chelonians, birds, and mammals, it is an endocrinic organ, contributing the products of its secretion to the blood stream.

IV. a. There is no direct relation between the parietal eye and the pineal body, but each is of itself an adaptive modification answering the demands for, or representing, an inherent impulse toward the development of a parietal eye, on the one hand, or a glandular organ, on the other.

b. The pineal body as it appears in mammals cannot be regarded as the vestigial or metamorphosed, degenerated or atrophic residuum of the parietal eye in vertebrates.

V. The phylogenetic significance of the parietal eye in vertebrates as the homologue of the median eye in invertebrates should be accepted with much reservation. Until such time as the homology between the vertebrate pineal region and some corresponding area of the invertebrate brain is much more firmly established than at present ,the parietal eye as an index in the evolution of the vertebrates from the invertebrates has but little value.—G. H.

Abstract Department

Two cases of ACHONDROPLASIA (Dos casos de acondroplasia). Cavengt (S.), Arch. Espan pedediat. (Madrid), 1919, **3**, 706-710.

A clinical history of two cases of evident achondroplasia in a girl of 13 years and a boy of 16 years. Radiography showed a normal sella turcica. Pluriglandular opotherapy was without result.—G. M.

ADRENAL HYPOPHYSEAL medication in asthmatic crises and the pathogenic considerations suggested (La médication adrénalino-hypophysaire de la crise d'asthme et les considérations pathogéniques quélle suggère). Bensaude & Hallion. Bull. gen. Therap. (Paris), 1920, **171**, 434-438.

The authors have made a study of the mechanism of the asthmatic spasm by recording the variations of respiratory expansion of the lung as influenced by intravenous injections of adrenalin and pituitary extracts. Adrenalin alone relaxes the bronchioles which explains the therapeutic efficiency of this drug in asthma. In very large doses the drug diminishes the respiratory expansion, however. This phenomenon is not attributable to a broncho-constriction but to an excessive congestion produced in the lung and consequent pulmonary edema. It it probable that all doses of adrenalin actually relax the bronchial musculature. On the other hand the hypophyseal extract is broncho-constricting in large doses,—doses much larger than would be used clinically. In small doses no appreciable bronchial spasm is produced: no restraint on the respiratory oscillations is observable; in fact they may be amplified. This latter effect of the pituitary extract is interpreted as the response of the lung to the lowering of the blood pressure induced in the pulmonary vessels. The decongestion of the lungs facilitates their expansion, which is diminished by the circulatory engorgement. The concurrence of these two effects, the relaxation of the bronchial musculature by adrenalin and the diminution of the pulmonary blood pressure by pituitary extract, is a justifiable explanation of the beneficial effects observed in their use in asthmatic spasms.—F. S. H.

The flow of ADRENAL blood in the dog (Sur le débit du sang surrénal chez le chien). Boncompte (J. T.), Compt. rend. Soc. de biol. (Paris), 1920, **83,** 1205-1206.

Measurements of the suprarenal blood flow have been made on animals the blood of which has been rendered incoaguable by peptone or hirudin. At the suggestion of Gley the author repeated the experiments on dogs simply anesthetized with chloral, and without anticoaglulant. The dogs weighed from 9.3 to 15 Kgs. A carefully sterilized canula was inserted into the left suprarenal vein.

The average of a number of determinations gave from 3 to 3.9 cc. per minute. Measurement of the blood flow during and immediately after stimulation of the peripheral and of the splanchnic of the same side (40 seconds' duration) in five expermients gave 1.9 cc.; 6.1 cc.; 5.4 cc.; 0.4 cc.; 4.3 cc. per minute. These results are so inconstant that more experiments must be made to eliminate the variable factors.—T. C. B.

ADRENAL hyperglycemia (Contribucion experimental al estudio de la hiperglucemia adrenalinica). del Campo (Clavero), Eco. med.-quir., 1920, —, — (Jan., Apr.).

The author's investigations confirmed those of earlier observers, to the effect that destroying the hepatic plexus in rabbits did not prevent adrenin hyperglycemia.—G. M.

ADRENAL hemorrhage in children (Apoplexie surrénale chez les enfants). Comby (J.), Arch. med. d' enf. (Paris), 1918, **21,** 651-656.

Five case reports are here presented of adrenal hemorrhage in children which is considered as either the direct or contributing cause of their death. The opinion is expressed that no treatment is availaing in true adrenal apoplexia.—F. S. H.

The musculature of the central veins of the ADRENALS in man. (La musculature des veines centrales surrénales de l'homme.) Dubreuil (C.), Compt. rend. Soc. de biol. (Paris), 1920, **83,** 1096-1098.

A description of the smooth muscle fibers of the suprarenal veins in man.—T. C. B.

(ADRENALS) Antibody production after partial adrenalectomy in guinea-pigs. Guenther (A. E.), Nebraska State M. J. (Norfolk), 1918, **3,** 15-19.

A general review with no new data.—F. S. H.

ADRENAL insufficiency and gastric ulcers (Insuficiencia suprarrenal y ulcera gastrica). Hernando (T.), An. de la Acad. med-quir. de Madrid, 1919, **6**, 378-400.

Many interesting clinical cases are described of gastric ulcers in Addisonians. A pathogenic relation is established between the two fundamental conditions by virtue of: (1) the lymphatic condition which accompanies the adrenal insufficiency, according to the investigations of Neusser and Wiesel, Marañón and others, and the frequency with which a large number of gastric ulcers are met with (Hernando, Arrese, De-Buen); (2) Disorders of adrenal insufficiency usually are vagotonic in nature and vagotonia predisposes to hypersecretion and that to ulcers (Eppinger); (3) In adrenal insufficiency there usually occurs, according to the studies of the author, free hydrochloric acid, an important condition in the pathology of ulcer; (4) In adrenal insufficiency infections are frequent, while Rosenow attaches great importance to infection in the pathology of ulcers. Admitting adrenal insufficiency as the predisposing pathological agent in ulcers, it is easy to explain several phenomena, such as the causative influence of fatigue and emotions, since fatigue uses up the circulating adrenalin, and emotion, which Cannon showed to be a factor augmenting the production of adrenalin, could very well result in using up of the same.—G. M.

Tuberculosis of the ADRENAL capsules in a man of twenty-six years. Death by cachexia (Tuberculose des capsules surrénales chez un homme de vingt-six ans. .Mort par cachexiè). Moutard-Martin (R.), Bull. et mem. Soc. med. d hôp. d. Par. 1917, N. S. **41**, 1161-1162.

A case report presenting no novel data. The weights of the adrenals at autopsy were 20 and 40 grams, respectively.

—F. H. S.

(ADRENAL) A case of Addison's disease. Oliensis (A. E.) & Mendelson (J. A.), N. York M. J., 1917, **105**, 156-157.

A more or less typical case of Addison's disease with marked asthenia and cutaneous pigmentation is described. Desiccated adrenal was given by mouth and adrenin was given intravenously but the case had advanced to such a stage that these measures were not fairly tested. The patient died one day after treatment was begun. At autopsy the adrenals were found to be tubercular.—I. M.

(ADRENAL THYROID) Addison's disease and exophthalmic goiter (Maladie d' Addison et goitre exopthalmique). Raymond (Félix), Bull. et mem. Soc. méd. d. hôp. d. Par. 1917, **41**, 1131-1138.

Report of a case of Addison's disease in a soldier of 26 years followed in 6 months by the onset of Basedow's disease. The author is of the opinion that a relation exists between the adrenal and thyroid function and gives a paragraph report of the favorable results he has obtained in treating Addison's disease by adrenal-thyroid opotherapy. The system of medication followed is to administer 0.5 gram adrenal powder and 0.1 gram thyroid powder twice a day for 6 consecutive days. The desiccated thyroid is then discontinued for 10 days while the adrenal preparation is still given, and on the 20th day a 10 days' treatment with the combined glandular products is again given. Beneficial results were obtained in 3 cases out of 22 treated.

—F. S. H.

(ADRENAL) Recent researches on the functions of the adrenal capsules (Quelques recherches récentes sur les fonctions des capsules surrénales). Roger (H.), Presse méd. (Par.), 1917, **25**, 665-668.

After reviewing briefly the important contributions already made to our knowledge concerning the function of the adrenals, the writer reports in this paper several interesting experiments carried out in his own laboratory. In the first of these an attempt was made to determine the pathological physiology underlying the clinically observed elevation of blood pressure in cerebral embolism or in apoplexy. Experimental cerebral embolism in rabbits was found to result in a marked increase in arterial pressure in decapsulated as well as in normal animals. However, in the normal animal the high level is maintained for a considerable length of time, while in the case of the one with adrenals previously removed the sharp rise was found to be followed almost immediately by a fall to normal or below. The author considers that this observation demonstrates an important role of the adrenals.

In a second experiment the relation of the adrenal secretion to vagus activity was studied. Stimulation of the peripheral stump of the cut vagus in the normal rabbit causes a slight lowering of blood pressure with a slowing of the heart rate to about 15 beats per minute, but the previous rate is promptly resumed upon removal of the stimulus. When the adrenals had previously been extirpated, such stimulation produced a greater depression of arterial tension and the slowing of heart rate was far more extreme (average interval of 29 seconds instead of

normal of 4 seconds between beats). In the decapsulated animal return to normal rate upon removal of the stimulating current was found to be greatly delayed. When the experiment on the decapsulated animal was repeated but with continuous injection of adrenalin, it was found that the results were almost identical with those on the normal animal. The author concludes from these observations that normally a tendency to inordinate action on the part of the vagus causes the adrenals to give off more of their secretion into the circulation, which in turn tends to balance the vagus overactivity.

The author further reports the discovery of a new substance in the adrenals, the action of which is antagonistic to that of adrenin. It is a black pigment precipitated by alcohol from the hot water extract of the whole gland. When redissolved in water made slightly alkaline with sodium carbonate and injected intravenously, it causes only a slight lowering of the blood pressure, but when such injection into a normal animal is followed by electrical stimulation of the vagus peripheral stump, the result is almost identical with that obtained in the case of the decapsulated animal. This substance is non-dializable and is alcohol insoluble, while the reddish brown pigment containing adrenalin is readily dializable and alcohol soluble.

The fact that injection of large doses of adrenalin causes an acute pulmonary edema suggests to the writer the possibility that over-activity of the adrenals in some terminal conditions may be the cause of this phenomenon. It was found that the edema fluid produced experimentally by injection of successive doses of adrenalin causes a definite rise in blood pressure when injected intravenously into other animals, whereas, edema fluid from the respiratory tract resulting from enormous injections of isotonic salt solution and isoviscous gum arabic solution has no such effect.—I. M.

ADRENALS, The relation of the spinal cord to the spontaneous liberation of epinephrin from the ——. Stewart (G. N.) & Rogoff (J. M.), J. Exper. M. (N. Y.), 1917, **26,** 613-656.

The purpose of the experiments reported in this paper was to determine the situation of the central nervous mechanism which sustains the spontaneous liberation of epinephrin from the adrenals. The method employed was that of severing the cervical and dorsal spinal cord of cats at various levels, testing adrenal blood before and again after section (from a cava pocket) for epinephrin. The denervated eye reaction of Meltzer, and rabbit intestine and uterus segments were used for detecting the epinephrin. It was found that section of the cord in the

level of the lowest cervical vertebra does not interfere with the liberation of the secretion which is in every respect the same as that obtained with the intact nervous system. After section of the cord in the mid-dorsal region the spontaneous liberation of epinephrin from the adrenals is abolished within the limits of detectability by the methods employed. The portion of the cord concerned in the liberation of epinephrin does not appear to extend much below the third thoracic segment.—I. M.

(ADRENAL) Contribution to the histo-pathological study of the suprarenal capsules and tetanic intoxication (Contribucion al estudio histopathologico de las capsulas suprarrenales de la intoxicion tetanica). Sabucedo (G.), Siglo méd. (Madrid), 1920, **67**, 230-236.

The author injected Indian rabbits with minimum lethal doses of tetanus toxin with the object of producing tetany of five or six days' duration. When the animal was about to die it was killed and the adrenals were promptly excised in order to avoid post-mortem alterations. In the cortical zone nothing of note was observed, but in the medulla necrotic lesions were found (chromatolysis, nuclear pyenosis) and diminution of the chromaffine substance, which indicated lack or scarcity of adrenalin. The importance of suprarenal exhaustion is demonstrated in death from tetany as observed by modern authors as is also the desirability of the employment of adrenalin as indicated by Marañón some time ago.—E. B.

Congenital lack of both ADRENALS and Addison's disease. Critical observations on the biochemistry of the adrenal system (Angeborenes Fehlen beider Nebennieren, und Morbus Addisoni mit kritischen Betrachtungen zur Biochemie des Adrenalsystems). Strauss (H.), Biochem. Ztschr. (Berlin), 1917, **79**, 51-67.

A description of a classical case of Addison's disease in which, at autopsy, no traces of the adrenal glands could be found. The case is interesting from the association of the lack of the adrenals and Addison's disease, and from the association of the Addison's disease with **status thymico-hypoplasticus** discovered at necropsy. The author discusses in some detail the necessity for more exact criteria in determining the extent of a deficiency of the adrenal system as a whole, but offers no particular solution for the problem.—F. S. H.

Massive hemorrhage of the ADRENAL in adult sixty-four years of age. Weidman (F. D.), Proc. Path. Soc. (Phila.), 1917, **37**, 3.

A description is given of a case in which a massive hemorrhage of the adrenal was found post-mortem in a man of 64. The veins showed extensive thrombosis and necrosis. The case is notable in that such hemorrhage, while common in the very young is seldom met with in the aged. The history notes did not refer to any symptoms that might be associated with this lesion.—I. M.

(ADRENIN) A survey of some elements of cardiac excitability. Burridge (W.), Quart J. Exper. Physiol. (Lond.), 1920, **12,** 355-366.

Among other factors, adrenin is considered in connection with cardiac excitability.—T. C. B.

(ADRENIN) Researches on the perfused heart: its mode of working. Burridge (W.), Quart. J. Exper. Physiol. (Lond.), 1920, **12,** 339-346.

Of endocrine interest in that the heart perfused with Ringer's solution is likened to a machine working without a lubricant. The normal lubricant is adrenin which facilitates certain actions of calcium. "Since blood contains adrenin, and Ringer's solution does not, the calcium tension of Ringer's solution must be higher than that of the blood to compensate for the absence of adrenin."—T. C. B.

Lethal dose of ADRENIN in man. (Beitrag zur Frage der für den Menschen tödlichen Suprarenindosis). Fischer (A. W.), Müchen. med. Wchnschr. 1920, **67,** 872-873.

Instead of novocain one cc. of a solution of adrenin 1:1000, was injected. Immediately after the injection the patient complained of severe pains in the neck and the head with tachycardia. The pupils first enlarged but later contracted. The pulse disappeared and death ensued. Post mortem examination showed status thymolymphaticus with poorly developed adrenal cortex. It is a question whether the status thymolymphaticus or the adrenin was the cause of the death.—J. K.

(ADRENIN) The influence of subcutaneous adrenin injections on the blood picture of normal and sick children (Der Einflusz subkutaner Adrenalininjektionen auf das Blutbild gesundes und kranker Kindes). Grimm (G.), Jahrb. f. Kinderh. (Berlin), 1919, **89,** 442-460.

Grimm studied the blood picture one-half and two hours after the subcutaneous injection of 0.5-1.0 mg. of adrenalin. He

found that the typical biphasic reaction occurred in sucklings as well as in older children and adults. This reaction comprises a rapid increase in the lymphocytes in the first half hour and its replacement within two hours by the picture of a polymorphonuclear leucocytosis. This reaction was not affected by intercurrent infections or extreme involvement of the lymph glands. It was also obtained after splenectomy. However, a weak reaction with absence of the lymphocytic phase was obtained in children of a "lymphatic constitution."—C. H. G.

The effect of ADRENALIN on muscular fatigue in Leptodactylus acellatus (L. Gir) and in Bufo marinus. Guglielmetti (J.), Quart. J. Exper. Physiol. (Lond.), 1919, **12,** 139-151.

Data published elsewhere. See Endocrin., **3,** 183.

ADRENIN injections intralaryngeally in the treatment of chronic bronchitis and bronchial asthma (Las inyecciones intralaringeas de adrenalina en el tratamiento de la bronquitis cronica y del asma bronquial). Gutierrez, Gamero & Acosta. An. de la Acad. med.-quir. de Madrid, 1919, **6,** 434-437.

The authors treated 20 cases of these disorders by intratracheal injections of 10 drops of adrenalin (1:1000) with great success. Daily injections for 2 or 3 days usually produced a cure.—G. M.

(ADRENIN) Studies on recovery from narcotics through injections into the heart (Über Wiederbelebungsversuche durch Herzinjecktion bei Narkosezufällen). Heydloff (E.), Monatsschr. f. Geb. u. Gyn. (Berlin), 1920, **51,** 318-330.

Summary of the literature and report of a case of collapse under morphin with cessation of heart-beat, recovery from which was induced by the injection of 2 cc. 1 per cent adrenalin solution directly into the heart through the 4th left intercostal space after massage had proved a failure.—F. S. H.

ADRENALIN administration by way of the alimentary tract. (De l'administration de l'adrénaline par la voie digestive). Lesné, Bull. et. mem. Soc. méd. d. hôp. d. Par. 1920, N. S. **44,** 800-801.

The intra-rectal injection of adrenalin in doses of 2 milligrams for children from 5 to 10 years old, and 3 or 4 milligrams for adults does not have a constant effect on the arterial pressure: it varies with the individual. At times there is a slow rise of the maximum tension and an augmentation of the oscillo-

metric index without modification of the diastolic tension. At other times a hypotension is observed. The maximum action is obtained in 15 to 20 minutes and all modifications disappear in an hour or an hour and a half.

But one should not judge the action of adrenaline solely on these paradoxical results, since it is regarded as certain that, given in large and fractionated doses, either by mouth or by rectum, this drug has a manifest influence on either chronic or acute adrenal insufficiency. The choice of the mode of introduction of adrenalin into the digestive tube is not without importance since its toxicity disappears when it is ingested, while when injected into the rectum it is toxic in the same doses as given subcutaneously. Although adrenalin is not altered by pepsin or pancreatin in vitro, the liver acts as a detoxicating barrier to the ingested drug, which barrier does not intervene to as effective an extent when intra-rectal administration is used. In view of these facts the rectal route is to be preferred whenever possible, for with small doses more rapid and efficacious results are obtained.—F. S. H.

ADRENALIN, The effects upon the blood pressure of the injection of—in dementia praecox. Lowrey (L. G.), Boston M. & S. J., 1920, **183,** 209-210.

The author, contrary to previous reports, did not observe a maintained blood pressure following the injection of adrenalin in cases of pubertas precox. In 54 of 60 of such cases there was an increase in the blood pressure following adrenalin. In 18 other psychopathic cases there was a depression in four.

—H. W.

Emotional reaction to ADRENIN (La reaccion emotiva á la adrenalina). Marañón (G.), Med. Ibera (Madrid), 1920, **145,** 353-357.

When small amounts of adrenin are injected into a subject, if the sympathetic system is sensitive, general and local phenomena are produced. The local reactions described by Goetsch are a zone of blanching around the point of injection, surrounded by a reddish zone and accompanied by erection of the hairs (goose-flesh). The general reactions which we described some ten years ago (Observations of the action of adrenin in man: Boletin de la soc. de biol. Madrid, June, 1911), are the well known changes in arterial pressure and carbohydrate metabolism and, in addition, motor phenomena (localized tremor of the hands extending to the arms and at times to the entire body); vaso-motor and secretory phenomena (pallor and reddening of the face, sweating, at times lachrymal secretion and

mild diuresis), and finally various subjective sensations (mild shivering, precardial oppression, feeling of respiratory oppression). All these phenomena are the same as those characterizing the emotions in general and are in accord with Cannon's hypothesis that a sudden secretion of adrenin into the circulation operates in the cause of the vegetative reaction to emotion. A sensitive subject, for example one with latent **hyperthyroidism,** when treated with adrenin, gives the syndrome of terror without having been terrified. At times this circumstance is recognized by the subject himself who declares of his own volition "It seems as if I was afraid but I am calm." This artificial reproduction of the emotion syndrome without emotion is very important and definitely refutes the classic hypothesis of Lange and James that emotion is the conscious perception of the vegetative phenomena of the emotional act. Nevertheless, at times the injection of the adrenin sensitizes the endocrine vegetative apparatus of emotion to such a degree that, in a centripetal manner, inversely to the normal, there is also produced a psychic emotion and the subject, after coolly perceiving the vegetative phenomena of emotion for some time, becomes psychically emotional. All the emotions produced by these injections are accomplished with great facility. For example, one of the female clinical patients spoke of her absent children, of the dangers they ran without her care, of the possibility that on her return this would be confirmed with sorrow, but all without emotion. Ten minutes after the injection of half a milligram of adrenin the same woman gave evidence of the physical signs of emotion induced by the drug, but entirely without psychic emotion; mention of her children, however, was sufficient immediately to arouse bitter weeping. This experience has been repeated in countless other cases with a distinct intensity according to the pathological and temperamental circumstances of the individual.

It appears as if adrenin can reproduce all the emotional syndromes except the psychic factor. This factor alone is lacking to emotional expression, and when we complete it with an emotional memory, which previously was insufficient to produce an emotional reaction because of the lack of sensitization by the somatic element, the emotion is produced in all its integrity.

This emotive action of adrenin occurs with extraordinary facility in **hyperthyroid** subjects, as Goetsch and others have demonstrated by the local reaction. It occurs also in other patients who clinically are not hyperthyroid, but in whom the vegetative system is excitable and unstable (emotional neuroses, neurasthenia, hysteria, epilepsy, menopause, etc.). Nevertheless it must be recognized that the majority of these cases have symptoms of latent hyperthyroidism. In reality this reac-

tion denotes the sensitiveness of the endocrine-vegetative system to emotion, a sensitivity which is found in all cases of excitability of the vegetative nervous system primarily and consecutively associated with endocrine disturbances, above all, those of hyperthyroidism and hyperadrenalism.—G. M.

ADRENIN content of the suprarenals in different diseases and a microchemical reaction for adrenin [Ueber den Adrenalingehalt der Nebennieren bei verschiedenen Krankheiten und mikrochemische Reaktionen von Adrenalin (Chromoreaktion Ogatsche Silbermethode)]. Ohno (S.), Verhandl. d .jap. path. Gesellsch. (Tokio), 1916, **6,** 15.

Ohno finds Ogata's silver method as satisfactory as the chrome reaction for determining the adrenin content of suprarenal substance. He investigated the adrenin content of the glands in the case of various diseases. The average amount of adrenin in the left suprarenal of man was 2.82 mg. Among all the diseases studied, the patients having beriberi had the greatest quantity of adrenin. In 5 cases this averaged 9.45 mg. The least amount was found in bronchial asthma. The quantity was fairly high in "contracted kidney," in 4 cases averaging 4.16 mg. The average in hemophilia (number of cases not stated) was 9.16 mg.—R. G. H.

The effect of ADRENIN upon the blood and splenic function (Die Adrenalinwirkung auf den Blut des Menschen, und ihre Beziehung zur Milzfunktion). Schenk (Paul), Med. Klin. (Berlin), 1920, **797,** 279; 309-312.

The injection of adrenalin in individuals showing a normal blood count and normal spleen, produces after 30 minutes a large increase of white blood cells, especially the lymphocytes, 14 to 24 per cent. A half hour later a polynuclear increase takes place. It takes six hours for the blood to return to normal. Injections of adrenalin into malarial patients causes an increased lymphocyte count together with an eosinophilia. The polynuclears are decreased. In tubercular states, injection of adrenalin is followed by an increase of red blood cells, haemoglobin and white cells, i. e., polynuclears, lymphocytes, large mononuclears and eosinophiles.—J. H. L.

The BLOOD SUGAR in narcosis and diseases of the nervous system. (Blutzucker Untersuchungen bei Narkosen und Nervenkrankheiten. Chantraine (H.), Zentralbl. f. inn. Med. (Leipzig), 1920, **41,** 521-529.

During ether narcosis the blood sugar is increased. This increase may range from 30 to 50 per cent. During narcosis with ethyl chloride the blood sugar remains unaltered. When the author experimentally produced concussion of the brain in rabbits by striking the heads with a hammer, no influence on the blood sugar could be detected. In patients with nervous diseases the quantity of blood sugar was the same as in normal persons.—J. K.

Tumor of the CAROTID BODY, excision with ligature of carotid arteries. Schley (W. S.), Am. Surg. (Phila.), 1917, **66**, 252-254.

A case of tumor of the carotid body with excision of the same along with the common, internal and external carotid arteries is described. The tumor was of twenty years' duration but had recently taken on an increased rate of growth. Its pathological nature and the symptoms, if any, produced by it are not described. Review of 75 cases of carotid tumor reported up to 1916 shows that of 54 cases operated upon 42 recovered from operation. Of these 42, 10 more cases died later from recurrences, local or metastatic, making 22 deaths in the operated cases.—I. M.

The early diagnosis of DIABETES. Addis (T.), J. Am. M. Ass. (Chicago), 1917, **69**, 109-111.

The chief emphasis of the article is laid on a functional test which is described. The patient, suspected of having early diabetes, is given 0, 25, 50, and 100 grams of glucose on four successive days. A positive reaction indicative of true diabetes mellitus is a sharply rising curve of sugar excretion. The urine is collected at the end of 2 and of 4 hours after each ingestion and sent to the laboratory for examination. The test is performed immediately after arising in the morning. The amount of water given with the sugar is uniformly one pint (500 cc.).
—R. G. H.

DIABETES, some personal equations and pathogenic coefficients in—. Anklesaira (B. N.), Indian M. Gaz. (Calcutta), 1917, **3**, 439-443.

The article is a picturesque amplification of the Bengalese adage, "No one is a gentleman who is not a diabetic at forty." Diabetes, according to the author, is a condition due to a long series of insults to the organism, and particularly to the alimentary canal. In his experience diabetes is always preceded by chronic constipation. The result of repeated violations of

hygiene is a slow intoxication which finally manifests itself as diabetes. The proper treatment is to reverse the etiological processes by diet, exercise, and general hygiene.—R. G. H.

DIABETES mellitus complicated with lipemia and xanthoma. Bates (L. B.), Proc. M. Ass. Isthmian Canal Zone (Mt. Hope), 1917, **9,** 49-52.

A case report. The patient, a white Jamaican woman of 34, came for treatment because of many fine, tender, discrete papules in the skin. Syphilis was suspected. When blood was drawn for a Wassermann reaction it was discovered that the serum was a creamy fluid. Routine examination of the urine showed sugar 5.8 per cent. An analysis of the blood showed ether extractives 6.34 per cent, of which 53.68 per cent was fat and 46.32 per cent cholestrin and other lipoids. The blood sugar was 0.10 per cent. The author adds that xanthoma is a rare condition, found chiefly in male subjects; of 36 cases reported 5 only were in females. The subjects are commonly of the florid, obese type, and nearly all have ranged between 25 and 50 years in age.—R. G. H.

Exanthema in juvenile DIABETES. (Exanthem bei kindlichen Diabetes). Bihlmeyer (G), München. med. Wchnschr. 1920, **67,** 720-721.

A child of six with serious diabetes showed a blueish exanthema. Death in coma resulted. Postmortem examination disclosed a diminished number of small islands of Langerhans but no other changes.—J. K.

El factor renal en la glucosuria y en la DIABETES. Bonilla (E.), Siglo méd. (Madrid), 1919, **66,** 883-885.

This is a study of the interventional conjunction of the renal factor in glucosuria. Reference is made to various cases of renal diabetes, characterized by the small amount of sugar eliminated, by the lack of influence of the dietary regime and by the absence of hyperglycemia. Treatment by "nefrina" is considered the most rational.—G. M.

(DIABETES) Observations upon the various types of diabetics under the present methods of treatment. Brigham (F. G.), Boston M. & S. J., 1920, **183,** 165-170.

Nothing new.—H. W.

DIABETES; the initial fast and tolerance testing. Brown (E. J.), Illinois M. J. (Chicago), 1917, **32,** 12-17.

Exposition of and practical comments on the Allen treatment. A general article, not amenable to abstracting.
—R. G. H.

Three cases of DIABETES. (Drei Diabetesfälle). Gerhardt, Müchen. med. Wchnschr. 1920, **67,** 888.

Demonstration of three patients who, though always showing glucosuria were markedly improved by a low protien diet.
—J. K.

Treatment of DIABETES complicated by pulmonary tuberculosis. Janney (N. W.), & Newell (R. R.), J. Am. M. Ass. (Chicago), 1920, **75,** 153-158.

These authors quote statistics regarding the frequency of tuberculosis among diabetics. They describe the clinical aspects of the association of diabetes and tuberculosis. The progress in treatment of these cases is considered at length. They summarize their findings as follows: the data presented indicate that the untreated diabetic is more likely to develop pulmonary tuberculosis than when maintained sugar-free by modern dietetic methods. In a series of sixteen diabetic cases complicated by pulmonary tuberculosis showing activity, twelve patients definitely improved during a course of institutional treatment; the diabetic symptoms improved in a majority of cases. The principles of the treatment recommended are the judicious employment of sufficient undernutrition combined with rest to maintain the patient sugar-free and control the tuberculosis. Fasting is unnecessary to obtain good results. Ill-advised fasting may lead to fatal outcome. Rest is at least as important as in the treatment of uncomplicated pulmonary tuberculosis.
—F. C. P.

The relation between DIABETES MELLITUS and clinical syphilis. Rosenbloom (J.), J. Am. M. Ass. (Chicago), 1917, **68,** 1232-1234.

A brief review of the literature dealing with the etiological relation of syphilis to diabetes and a report of sixty-two cases of diabetes mellitus studied from this angle. R. found positive evidence of syphilis in 10.3 per cent of these cases, but since none of those who received antisyphilitic treatment showed an increase in tolerance for carbohydrates, it is concluded that there is no etiological relationship between them and that the two diseases exist independently.—I. M.

DIABETES in children. Joslin (E. P.) & Gray (H.), Med. Rec. (N. Y.), 1917, **92,** 40.

This communication deals with diabetes in children as regards etiology, improvement in prognosis and treatment, based upon analysis of 123 cases under 15 years of age. In a high percentage of cases obesity, lack of exercise and infections were considered of prime importance as regards etiology. With the better treatment the prognosis is not so hopeless as it was formerly considered to be. Of 53 cases that had been under Joslin's supervision 31 were dead and 15 were still living in one series, while of the other 7 cases 2 were dead and 5 living, making an average duration of over 5 years.—I. M.

The blood lipoids in DIABETES. Joslin (E. P.), Bloor (W. R.) & Gray (H.), J. Am. M. Ass. (Chicago), 1917, **69**, 375-378.

The authors made a complete analysis of the blood lipoids in 131 samples of blood from 87 diabetic patients by Bloor's fat method and compared them with 23 analyses of blood from normal individuals. The three lipoid fractions (total fatty acids, lecithin and cholestrol) were determined separately in each case, not only in the whole blood but in the plasma and in the corpuscles as well. It was found that all grades of diabetes are distinguished by a marked increase in lipoids of the blood and the increase is progressive with the seriousness of the disease. The average normal blood lipoid level is 0.59 per cent. In mild diabetes the average is about 0.83 per cent, in cases of moderate severity 0.91 per cent, and in severe cases about 1.41 per cent. The highest value found was 16.3 per cent, which was found in a very severe case. Although the total of fatty acids is trebled, the cholesterol is only doubled and the lecithin is increased but one-third. The increase in cholesterol is particularly significant in that it seems to be pathognomonic of prolonged diabetic hyper-lipemia. The variation in the lipoids takes place chiefly in the plasma, the corpuscles of diabetics showing little or no increase in lecithin and cholesterol over the normal. No difference was found in diabetics with and those without nephritis. Cases with acidosis showed a higher level of total lipoids than those without acidosis and cases with moderate acidosis showed a much higher lipoid level than others with severe acidosis. There seems to be a normal blood-lipoid threshold similar to that for sugar. This is about 0.67 per cent. The lipoids decrease with fasting and increase on a diet of fat or carbohydrate. It was found also that the blood lipoids do not rise and fall with changes in blood sugar. The blood lipoid level is a much more accurate test of the severity of diabetes than is the sugar content. High lipoids indicate a grave prognosis.—I. M.

Reaction to pyrogenetic substances as a constitutional index with especial reference to DIABETES mellitus (Ueber pyrogenetisches Reactionsvermögen als konstitutionelles Merkzeichen, unter besonderer Berücksichtigung des Diabetes mellitus). Schmidt (R.), Ztschr. f. klin. Med. (Berlin), 1918, **85,** 303-318.

The experiments reported were undertaken to study the constitutional reaction of different individuals, especially diabetics, to pyrogenetic agents. Various protein preparations, such as milk, deuteroalbumose and tuberculin were injected subcutaneously, the temperature being taken before and for some time after the injection. It was found that different individuals differ widely in their reactions to the same pyrogenetic agent, some showing a prompt and constant response while others react but slightly or not at all. From the latter the author assumes the existence of what he calls an "afebrile diathesis," which is manifested most commonly in individuals who show other stigmata of metabolic degeneration.

Diabetics examined were found to respond but slightly or not at all. While there is no direct parallel between the body temperature and degree of hyperglycemia, the inability of the body to metabolize carbohydrates efficiently seems to be closely associated with this "afebrile diathesis."—I. M.

(DIABETES) The blood sugar during a voyage from Holland to India. (Over het bloedsuikergehalte tijdens de reis Holland-Indie). Schut (H.), Geneesk. Tijdschr. v. Ned. Indie (Batavia), 1920, **60,** 424-429.

In the tropics the amount of blood sugar is about 30 per cent higher than in Holland. When people with this large quantity of sugar go on the mountains or make a voyage, the blood sugar becomes normal. The so-called "low fever" frequently observed in India may be considered as an effort of the body to oxidize the surplus of sugar. The author examined the blood of people making a voyage from Holland to India. As long as they are on sea the amount of sugar is not increased, even when they are in the tropical seas. It was possible to examine three mild cases of diabetes in all of which the glycosuria disappeared during the voyage.—J. K.

The association between DIABETES MELLITUS and tuberculosis Solis-Cohen (S.), Med. Rec. (N. Y.), 1917, **92,** 40.

This is a brief expression of opinion on the relationship of these two diseases. While there are no reliable statistics and no other data pointing to a definite relation between them, the

author points out that the family histories of cases show certain facts which indicate some fundamental association. This is vaguely referred to by the terms constitutional, congenital or hereditary in these conditions. Diabetes is likely to eventuate in tuberculosis.—I. M.

DIABETES and eucalyptus (L'eucalyptus et le diabéte). Trabut. Bull. gén. therap. (Paris), 1920, **171,** 429-430.

Good results are reported in the treatment of diabetes, but no specific citations made, from the use of a decoction of 10 to 15 grams of eucalyptus leaves (species: E. globulus; E. diversicolor; E. rostrata) per liter of water boiled down to small volume. The amount administered is not given.—F. S. H.

(DIABETES) The relation of the acid-base equilibrium of the body to carbohydrate metabolism and its application in human diabetes. Underhill (F. P.), J. Am. M. Ass. (Chicago), 1917, **68,** 497-500.

The literature dealing with the effects of various agents on the blood sugar and glycosuria is briefly discussed. From the experimental work done along this line it is clear that a condition of acidosis facilitates the elimination of carbohydrates from the body, whereas in alkalosis there is a tendency to conserve carbohydrates. The author applies this idea to the treatment of cases of human diabetes, pointing out that the conventional diabetic diet consists mainly of acid producing foods, such as meats, fats and cereals, which aggravate the condition of acidosis. A severe case of diabetes was treated over a period of two years with definite benefit to the patient. Milder cases likewise respond favorably. Alkali was given as sodium bicarbonate in carbonated water in quantities just sufficient to keep the reaction of the urine near the point of neutrality to litmus. It was divided in seven equal doses and given at intervals throughout the daylight hours.—I. M.

A study of the significance of heredity and infection in DIABETES MELLITUS. Williams, (J. R.), Am. J. M. Sc. (Phila.), 1917, **154,** 396-406.

The author considers in some detail the relation between the various so-called degenerative diseases, diabetes mellitus, arteriosclerosis, cancer and nephritis. He points out that they appear to be in a sense products of civilization in that they are almost unknown among nomadic peoples living in a primitive state. He cites statistics to show that these four conditions have increased tremendously in frequency within the past few

decades. With the view of determining the relation of arteriosclerosis, obesity and cancer to diabetes and to throw more light on the hereditary element in diabetes, he obtained full data regarding all relatives of 100 cases of diabetes mellitus and of 100 non-diabetics suffering from gastro-intestinal or other common disturbances. The evidence strongly indicates the possibility of infection as an important factor in precipitating the metabolic collapse recognized as diabetes. The writer concludes that the liability to diabetes and arteriosclerosis is transmissible from parent to child and emphasizes the importance of safeguarding individuals with family history of such conditions from all infections.—I. M.

(DIABETES MELLITUS) The effect of undernutrition on muscular force; a study of the influence of low diets, or the Allen method of treatment on the physical vigor of diabetics. Williams (J. R.), Arch. Int. Med. (Chicago), 1917, **20**, 399-408.

An interesting study is reported in which the muscular vigor of a number of diabetics was tested by means of the Collins dynamometer while receiving different diets, to show the effect of the Allen method of treatment on the muscular strength. The common clinical observations that diabetics as a rule are distinctly weaker physically than normal individuals was confirmed. There was shown to be a direct relationship between food tolerance and muscular vigor. The continued use of a low diet for many months, even though it falls short of the energy requirements of the body, provided it is within the physiological limitations of the body to metabolize it, will cause an appreciable gain in muscular tone, although the amount of physical effort that such a person may be able to put forth may be considerably below the normal. This is in accord with the clinical experience that nutrition within the tolerance of the patient gives the greatest comfort, strength and sense of well being. The investigation shows also that while diabetics living on a diet below normal physiologic requirements possess a diminished muscular power, feeding them beyond metabolism limitations causes not only a further reduction in their tolerance for food but also an even greater loss of strength.

The general conclusion is drawn that diabetics gain in physical vigor as they become and remain sugar free, while over-feeding causes a definite and often a serious loss of strength.—I. M.

A fatal case of DIABETES MELLITUS associated with large-cell hyperplasia. Williams (J. R.) & Dresbach (M.), Am. J. M. Sc. (Phila.), 1917, **153**, 65-78.

A fatal case of diabetes mellitus is described in which the pancreas was found to be practically normal while the lymph nodes, liver and particularly the spleen showed the presence of large-cell hyperplaisia. This is the fourth case of the kind on record. Examinations of the formalin fixed sections by means of specially stained frozen sections and by means of the polariscope revealed the presence of extensive deposits of lipoids. The hyperplasia in these cases is said to resemble the cell changes in Gaucher's disease of the spleen in some ways but the large cells found in the latter condition do not contain the deposits of lipoid material. Furthermore, Gaucher's disease is a familiar disease while the condition discussed in this paper is not. A brief discussion of the newer ideas of fat metabolism is also given.—I. M.

The treatment of DIABETES MELLITUS. Williamson (R. T.), Lancet (Lond.), 1917, **1**, 650-652.

The author describes five different graded diets which he employs in uncomplicated cases of diabetes mellitus. If in a given case the glycosuria does not disappear within a few days on one of these diets, another is selected and given a trial. If none of them improve the condition within a week's time, he institutes fasting days, on which the patient is allowed only tea or coffee, beef tea, or whisky-and-soda. When the diets fail to check the glycosuria after a satisfactory trial, he resorts to the use of drugs such as sodium salicylate, aspirin or quinine salicylate. He claims to have clearly demonstrated the ability of these drugs to diminish the glycosuria in mild and moderately severe cases. Potassium bromide is also given in cases suffering from insomnia or marked neurasthenia. The ordinary rigid diabetic diet is said by this writer to be unsuited to cases with persistent acidosis and should be supplemented with a small amount of carbohydrate, while meat is to be restricted.
—I. M.

Observations upon DUCTLESS GLAND therapy. Lawrence (C. H.), Boston M. & S. J., 1920, **183**, 160-165.

The author believes that though the symptoms of early stages of endocrine disorders are often polyglandular in character, there exists a "characteristic and recognizable syndrome for a primary derangement of each individual gland." The recognition of the syndrome is essential for the intelligent administration of glandular therapy. This belief is apparently based upon the following case report. A nurse 37 years old, since the age of 13 had suffered attacks of "hay-fever" with asthma for the last 3 years. Cutaneous tests were negative to

pollens but positive to meat, milk, several kinds of fish, many vegetables, chocolate and coffee. Removal of these from the diet eliminated the asthma, but she could not maintain weight. She was troubled a great deal with extreme sleepiness irrespective of the amount of rest secured. At 16 years of age the patient rapidly grew tall, but was never weak or nervous. These and other factors led the author to suspect pituitary dysfunctioning. She was given whole pituitary and advised to eat anything desired. As long as pituitary substance was taken anaphylactic symptoms did not occur although the diet was general. Omission of the therapy was always followed within 48 hours by a return of the anaphylactic symptoms.—H. W.

The pharmacology and therapeutics of the DUCTLESS GLAND preparations. Sajous (C. E. de M.), Penn. M. J. (Athens), 1917, **21**, 178-184.

The writer discusses in some detail the normal functions and the disorders of the **adrenal, thyroid** and **pituitary** glands and the therapeutic uses of the preparations derived from them. It is his opinion that the adrenal secretion, while passing through the lung capillaries, takes up oxygen and becomes a constituent of hemoglobin. To this new constituent, termed by him adrenoxidase, is attributed catalytic properties, by virtue of which it sustains oxidation within the tissues of the entire body when carried to them by the blood stream. This respiratory function is the fundamental principle of the therapeutic application. When, therefore, the secretory activity of the adrenals is more or less inhibited toward the end in infectious diseases, the use of adrenalin is indicated and is often a great life-saving measure. Its striking effects in relieving attacks of bronchial asthma are claimed to be due to this property and to its power to evoke a defensive reaction through which the poisons causing the bronchial spasm are broken down.

As opposed to the secretory theory of pituitary function, the author maintains that its function is to protect the body against certain intoxications by enhancing the activity of the other ductless glands, notably the adrenals and thyroid. The organ is viewed as a chief co-ordinating nervous center or ganglion of the sympathetic system. The anterior lobe is looked upon as a contractile body much as is the spleen. According to the theory, it periodically projects a serum-like fluid, containing the contents of red and white cells, over a layer of sensory cells resembling those of the nasal olfactory area. When this fluid contains certain poisons, the sensory cells react and excite the ductless glands to inordinate activity

through sympathetic nerve paths. As evidence for this theory he recalls cases of acromegaly in which hyperthyroidism is a prominent accompaniment of the erethic stage, whereas in the asthenic stage signs of myxœdema and Addison's disease appear. The therapeutic effect of pituitary substance is attributed to its content of adrenal principles which combined with nuclear bodies gives it a long list of uses.

The function of the thyroid is said by the author to be closely related to the phenomenon of immunity and through the over stimulation of this defensive mechanism by infectious thyrotoxicoses are initiated. Thyroidectomy should, therefore, be done less frequently in these conditions and removing of foci of infection resorted to more frequently.—I. M.

ENDOCRINE disturbances of syphilitic origin (Alteraciones endocrinas que tienen un origen sifilitico). Albadalejo (L.), Estudios med. (Murcia), 1920, pp. 3-17.

Syphilis frequently produces lesions of the endocrine glands, at times directly (as conjunctival infiltration gumma) and at times indirectly as in one of the author's cases with syphilitic lesions of the sella turcica which involved the **hypophysis**. Just as the **adrenals** are very sensitive to tubercular infection, so are the **thyroid** and **hypophysis** sensitive to syphilis. In such cases opotherapy has only a relative efficacy depending on a complementary anti-syphilitic treatment. Four cases of syphilitic endocrine lesions are described with syndromes of **thyroid** insufficiency in two, and of hypophyseal insufficiency in two.—G. M.

(ENDOCRINE GLANDS) Tetany in children. Payne (W. W.), Guy's Hosp. Gaz. (Lond.), 1920, **34**, 106-108.

The relationship of the ductless glands (particularly the parathyroids) to calcium metabolism, is reviewed in this paper.
—J. H. L.

ENDOCRINE ORGANS as factors in the treatment of skin diseases (Die sich aus den Einflusz der endokrinen Drüse ergebenden therapeutischen Gesichtspunkte bei Erkrankungen der Haut. Pulay (E.), Therap. Halbmonatsh. (Berlin), 1920, **34**, 302-305.

The sexual organs have a certain influence on the skin. Seborrhoea becomes more marked at puberty; infection with microsporon audouini in children is nearly incurable but in puberty it disappears without any treatment. A dermatitis symmetrica dysmenorrhoica has been described. All kinds of skin dis-

ease may be influenced by menstruation. The pigmentation during pregnancy is well known. Seborrhoea often disappears during pregnancy. In myoma of the uterus loss of hair has often been observed. Skleroderma beginning at the menopause has been described. All these facts point to the existence of relations between the skin and gonads. But we must not expect too much from treatment with ovary or corpus luteum in skin disease. There are only a few cases known in which a skin disease during pregnancy has been cured with corpus luteum.—J. K.

(ENDOCRINE ORGANS) La Emocion. Turro (R.), Siglo méd. (Madrid), 1919, **66,** 1074-1076.

A review and criticism of the different theories concerning emotion. In the first period of the development of this study, the psychological theories regarded the emotions as having an organic origin determined by psychic states. Turro justly states that these ideas do not permit of a clear view of this intricate subject. Later there appeared a modern phase that we may call physiological, which affirms the existence in emotion of an organic base which presents itself in all emotional manifestations that the organism is capable of producing experimentally without intervention of a psychic factor. These modifications are engendered by the endocrine organs so that it can be affirmed that emotion involves a passing endocrine crisis characterized by hyperthyroidism and hypersuprarenalism on the one hand, and hypopituitarism on the other. This crisis may become so intense as to assume a permanency which gives rise to emotional diseases. The critical stage of permanent emotionalism has been admirably described by Marañón. The psychic impressions tend to influence the endocrine system and give origin to its manifestations; hence, if we inject **adrenalin** in a subject affected with **hyperthyroidism,** there is brought about an emotional crisis that is purely "endocrine", the subject not exhibiting psychic emotion (Marañón). If the excitation is very great, the subject becomes autoemotional, the humoral current proceeding in the direction of the psychic centers. According to Achucarro, the nerves may be the point of union between the psychic and endocrine elements which intervene in all emotions. Turro seems to be in complete accord with this view and method of clearing up the problem of emotion.—E. B.

ENDOCRINE origin of some intestinal changes. (Algunas alteraciones intestinales de origen endocrino). Hernando (T.), An. de la Acad. med.-quir. (Madrid), 1919, **6,** 17-37.

The author presents an extensive study of the question together with a complete bibliography. He studied primarily the diarrheas of Graves' disease which he considers of vagotonic origin, since he was able to produce them by injection of pilocarpine and stop them by atropine. In some cases also he was able to influence the production of the hyperchlorhydria. He calls attention to the frequency of these diarrheas of **thyroid** origin, which are not always well diagnosed and are resistent to the usual treatment, yielding well, on the other hand to atropine and to adrenin enemas. He further studied the diarrheas of adrenal insufficiency, characteristic of Addison's disease and the frustrated forms of adrenal insufficiency. In the second part he discusses constipation in the endocrine states. In certain pathological conditions of the **hypophysis** constipation occurs, at times due to the lack of the hypophyseal hormone which stimulates intestinal contractility. Given the inhibitory effects which adrenin exerts on the intestinal motility, it is logical to suppose that there will be constipation in those pathological conditions in which an excess of adrenin is produced. The constipation of the arteriosclerotics, and above all of women during the menopause can be attributed to this factor, which agrees with the ideas of Culbertson and Marañón. Hernando finally takes up the constipation of **hypothyroid** disturbances. In some of these cases this symptom was almost the only one of athyroid disorder, and it rapidly improved under opotherapy. He accepts, as an explanation of the hypothyroid constipation, the hypothesis of Levi and Rothschild, according to which the lack of thyroid secretion produces an increase in the concentration of the calcium ion, to which is due the diminution of the neuromuscular excitability of the intestine, which in turn influences the lack of tone of the vagus.

—G. M.

ENDOCRINE therapy of ozena (Endocrinoterapia del ozena). de Olavarria (L.), Rev. Españ. de laring. otol. y rinol. (Madrid), 1919, **7**, 56-86.

The author studied 120 cases of ozena and found that 65 per cent of the subjects were affected with disturbances of menstruation of hypophyseal and dysthyroidal origin. In all such he used **ovarian, thyroid** and **hypophyseal** opotherapy, and if disturbances of growth were evident, thymus was included. The results obtained were very satisfactory, 37 of the 107 treated having been cured. According to his statistics ozena predominates in the female sex, appearing in the pubertal period and reappearing at the menopause, becoming attenuated during pregnancy and increased during menstruation. Frequently

obesity accompanies the disorder. All of these data speak in favor of an endocrine factor in ozena.—G. M.

Contribution to the etiology of ENDOCRINE syndromes (Contributo all 'etiopatogenesi delle sindromi endocrine). Pentagna (O.), Pediatria (Naples), 1920, **28,** 455-469.

The author analyses 115 cases of endocrine disturbance observed in the Naples clinic since 1914, among a total of twenty thousand children examined. In 46 per cent of the cases syphilis was found, either in the patient or in the parental anamnesis. Pentagna concludes, therefore, that syphilis may be an important etiological factor in determining endocrine dysfunction. The influence of lues is not interpreted as being a direct syphilitic manifestation but rather as due to the action of the syphilitic toxins during embryonal life, producing congenital alterations in the endocrine glands. Later in life this alteration manifests itself as a dysfunction.—G. V.

(ENDOCRINOLOGY) The psychology of INSANITY (La psicología de la locura). Delgado (Honorio F.), Crón. Méd. (Lima, Peru), 1919, **36,** 675; Abst., J. Am. M. Ass., **74,** 565.

Delgado remarks that experience has shown the important part played by moral factors in the development of mental derangement; in fact, he deems this the principal factor. Of course every psychic process has its molecular concomitant, but Delgado reiterates anew "the priority of the function—the conception which is rejuvenating medicine in all its branches now." "Modern endocrinology is also demonstrating the connection between the psychologic activity and the somatic activity, and the influence of one on the other."

Review of the past year's literature on ENDOCRINOLOGY. (Jaaroverzicht van de literatuur over de klieren met inwendige afscheiding). Stuurman (F. J.), Nederl. Maandschr. v. Geneesk. (Leiden), 1920, 1, 401-420.

A good review.—J. K.

(ENDOCRINOPATHIES) A peculiar variation of Bloch's syndrome (Una curiosa variante del sindrome de Bloch). Juarros (C.), Siglo méd. (Madrid), 1920, **67,** 417-418.

The author makes note of the frequency with which endocrine factors intervene in the psychoneuroses, holding it necessary to make a careful study of patients in order to avoid confusion with respect to diagnosis of hysteria and neuras-

thenia. He describes the symptomatology of Bloch's syndrome and refers to the case of a woman who presented this syndrome during a prolonged absence of her husband and who also manifested signs of **hyperthyroidism** which disappeared following employment of **ovarian** preparations and antithyroid serum.
—E. B.

(GENERAL) The relationship of the external appearance of the body to disease. Draper (G.), N. Y. State J. M. (N. Y.), 1920, **20,** 273-279.

An interesting article in which the author attempts to show that the endocrine organs are to a large degree responsible for the external appearance not only in health but also in disease. Physiology, anatomy, psychology and immunity are considered the "four panels" primarily representative of life; the proper correlation among these is influenced by and to a great extent determined because of the endocrine functioning. Diet, toxins and environment are factors which influence the harmonious balance between the "four panels" and the endocrine organs, any imbalance resulting in characteristic alterations of the bodily structure and its functions.—H. W.

GLANDULA INSULARIS. Luksch, Deutsche med. Wchnschr. (Berlin), 1920, **46,** 900; Wiener klin. Wchnschr., 1920, **33,** 743.

Luksch reports the autopsy findings in the case of a woman who died at 34. In the neck and in the axillae were found bits of tissue which, upon histological examination, were seen to consist of cells in the form of islets without surrounding capsule. Pende has previously described this structure under the name of "Glandula insularis." He assumes that it has **an** endocrine function. Pende found the gland both in children and in puppies. Kohn has taken issue with Pende and regards the structure as merely an early form of fatty tissue. Luksch does not hazard an opinion as between these two.—J. K.

GLYCOSURIA during pregnancy. Hitchcock (C. W.), J. Mich. M. Soc. (Detroit), 1920, **19,** 399-404.

Lactosuria is common during both pregnancy and the puerperium. This condition is entirely physiological and must be differentiated from the various types of glycosuria. From 30 to 50 per cent of pregnant women are less tolerant to glucose than non-pregnant women. Such cases do not show hyperglycemia and, therefore, are not diabetic. True diabetes, of course, may be present in pregnancy.—H. W.

(GONADS) A case of hermaphroditism verus bilateralis in a goat (Een geval van hermaphroditism verus bilateralis bij de geit). Kredit (G.), Tijdschr. v. Diergeneesk. (Utrecht), 1920, **47,** 134-139.

Testicular tissue was found in both ovaries of a goat. The organs did not show any sign of ovulation. —J. K.

Disturbance of the endocrine function of the GONADS Quimby (W. C.), N. Y. State J. M. (N. Y.), 1920, **20,** 279-281.

Case reports. I. Precocious puberty in a girl of seven years associated with a tumor of the ovary (hypergenitalism). Following a fall at the age of four years bleeding from the vagina occurred, which was not associated with pain; the breasts enlarged and pubic hairs appeared. Bleeding from the vagina occurred again at six and a half years and at seven. This last period was associated with pain, nausea and vomiting. The sella was normal; the Wassermann reaction was normal. A tumor of the right ovary was removed. No post-operative history is given.

II. Delayed puberty; associated with possible hypophyseal dysfunction (hypogenitalism). A girl of 16 years had never menstruated. She suffered from polydipsia and polyuria and fainting spells; she was never strong; growth was stunted; her height was 49 inches at 16 years. Secondary sex signs were moderately developed. No hypophyseal tumor was shown and the patient passed from under observation.—H. W.

(GONADS PLACENTA) Substances which actively regulate the growth of the genitals (Substanzen, die das Wachstum des Genitales wirksam anregen). Schröder, Monatsschr. f. Geb. u. Gyn. (Berlin), 1920, **51,** 433-434.

The question of infantilism is bound up with the lack of stimulation to growth of the genitals. The interstitial cells of the ovary are important. Schröder was able to get enormous development of the genital canal in growing animals by injection of a **placenta** preparation. In male animals the utriculus masculinus alone hypertrophied. The substance accordingly is not specific but acts on both sexes. A substance acting similarly was obtained from the liver, but none was found in the spleen. Schröder is of the opinion that the compound is a cholesterol. Whether or not it is a hormone he is not sure. Its action in cases of infantilism is yet to be studied.—F. S. H.

(GONADS) Hermaphroditism in man. Sheppard (H.), Anat. Rec. (Phila.), 1920, **19,** 55-65.

Published previously in abstract. See Endocrin., 1920, **4**, 460.

(HYPOPHYSIS) Hypophyseal changes in experimental diphtheria infection (Über die Hypophysenveränderung bei experimentellen Diphtherieinfection). Adachi (O.), & Tanaka (K.), Verhandl. d. jap. path. Gesellsch. (Tokio), 1916, **6**, 23-24.

The authors infected guinea-pigs and rabbits with Bacillus diphtheriae. The hypophysis of each was then subjected to histological examination. It was found that the pars intermedia reacted to the intoxication more than did the remainder of the hypophysis. The cell boundaries were indistinct and the nuclei pycnotic. In case of the more severe reactions only granular masses remained in place of the cells. Often necrotic masses were seen in the intermediate zone, which was otherwise relatively little changed. Near the juncture of the anterior lobe and pars intermedia a confluence of the cells was often observed. In the anterior lobe the granules of the eosinophile cells in many cases had disappeared. In some there were round-cell infiltration and necrotic areas. The posterior lobe was relatively little changed. The changes described were found in animals dying from the infection within three to fifteen days. In general, the guinea-pigs reacted more than did the rabbits.—R. G. H.

Experiments in the transplantation of the HYPOPHYSIS of adult Rana pipiens to tadpoles. Allen (B. M.), Science (N. Y.), 1920, n. s. **52**, 274-276.

Grafts of three kinds were used, viz., anterior lobe, intermediate lobe and combined intermediate and posterior lobes. The graft was thrust into a pocket under the skin above the right eye. Three hundred and eighty-four operations were performed. 1. "The anterior lobe transplanted to normal, to pituitaryless, and to thyroidless tadpoles in each case produces a marked acceleration of growth so that the tadpoles thus treated are conspicuously larger than those into which the other parts of the hypophysis have been transplanted. They are larger than normal controls and larger than controls into which muscle tissue has been transplanted in the same way and at the same time as the above operations." 2. "Normal tadpoles into which the intermediate lobe is engrafted become much more darkly colored than the controls, while those which have been made to turn white as a result of removal of the anlage of the hypophysis exclusive of the posterior lobe are

made to change back from white to black when the intermediate lobe is engrafted into them." 3. Tadpoles into which the combined intermediate and posterior lobes are transplanted show not only the color change mentioned above but they also suffer a marked contraction of the body walls. Within twelve hours they appear very emaciated. This characteristic gradually disappears, in the course of ten days. These tadpoles show apparent retardation of growth. When the intermediate and posterior lobes are dissected apart and transplanted separately it is seen that this phenomenon is due wholly to the posterior lobe. It is probably caused by the well-known property that this portion of the hypophysis possesses of bringing about muscular contraction. The following conclusions are justified: 1. The anterior lobe of the hypophysis stimulates growth and metamorphosis: 2. The intermediate lobe is very largely if not wholly concerned in regulating such color changes as are controlled by the hypophysis; 3. The posterior lobe causes marked contraction of the body walls and at least apparent retardation in growth.—F. A. H.

(HYPOPHYSIS) Early diagnosis of early pituitary tumor with ocular phenomena. Benedict (W. L.), Am. J. Ophthal. (Chicago), 1920, **3,** 571-584.

Pallor of the discs and changes in the visual fields should always excite suspicion of pressure processes, the etiology of which should be less hastily ascribed to tabes and other neuritic processes. Ocular phenomena develop early in cases of pituitary tumor. The decision as to operation should properly rest on changes in the visual field and appearances of the optic disc since the indications for operation disappear with the development of optic atrophy.—H. W.

HYPOPHYSEAL cachexia in a case of cancer of the HYPOPHYSIS (Uber hypophysäre Kachexie bei Hypophysenkarzinom). Budde, München. med. Wchnschr., 1920, **67,** 826-827.

A woman of 27 showed swollen glands in the neck; after removal and x-ray treatment the tumor began to grow again and now very rapidly. Histological examination showed the tumor to be a carcinoma. Three months after these symptoms began there were observed symptoms of increased brain pressure, loss of pubic and axillary hair, loss of pigment of the hair of the head, with pigmentation of the linea alba and amenorrhea. Autopsy disclosed cancer of the hypophysis, destroying the whole gland and metastases in the lungs. Tumors of the hypophysis rarely give rise to metastasis in other organs. It is

extremely rare that symptoms caused by the metastasis are observed preceding those from the hypophysis. Only one previous case of this type has been published.—J. K.

(HYPOPHYSIS) Pituitrin in obstetrical practice (Pituitrine in de verloskundige praktyk). Catz (B. F.), Nederl. Maandschr. v. Geneesk. (Leiden), 1920, **1,** 377-382.

Description of 8 obstetrical cases in which pituitrin was of great value.—J. K.

(HYPOPHYSIS) Pituitrin. Conley (A. A.), Journal-Lancet (Minneapolis), 1917, **37,** 505-507.

Conley reports very satisfactory results from the use of pituitrin for deflation of atonic intestines, emptying of atonic bladders, and as a uterine stimulant.—R. G. H.

(HYPOPHYSIS) Hypophyseal cachexia. Remarks on syphilis of the pituitary (Ueber hypophysäre Kachexie; ein kasuistische Beitrag zu Syphilis der Hypophysis. Feit (Herman), Med. Klin. (Berlin), 1920, **16,** 421-422.

Report of a luetic individual manifesting symptoms of hypopituitarism and cachexia. The face was yellow and beardless, the voice boyish in timbre and the genitals were undeveloped. A history of polyuria and polydipsia was given. The blood showed 50 per cent small lymphocytes, 5 per cent large lymphocytes, 43 per cent polynuclears and 2 per cent eosinophiles. No changes in the sella were seen. After two salvarsan injections his subjective symptoms improved, his strength came back, and the polyuria and polydipsia disappeared. A gain in weight is recorded. His increased lymphocyte count was not altered.—J. H. L.

(HYPOPHYSIS) Dystrophia adiposogenitalis. Foerster, Deutsche med. Wchnschr. (Berlin), 1920, **46,** 1066.

Demonstration of a man of 37. Seventeen years ago he became fatter; 12 years ago the penis became smaller and the patient became impotent. He complains now of severe headaches, of ready fatigability and of a general feeling of being ill. The breasts are of the female type. The roentgenogram shows an enlargement of the sella turcica.—J. K.

The HYPOPHYSIS and its active principles. (Die Hypophyse und ihre wirksamen Bestandtheilen). Fühner (H.), Deutsche med. Wchnschr. (Berlin), 1920, **46,** 1066; Therap. Halbmonats. (Berlin), 1920, **34,** 437-442.

A general review on the physiology and pathology of the hypophysis. Most commercial preparations (pituitrin, coluitrin, pituglandol) are simply extracts from the cow's gland. Hypophysine (Hoechst), however, is a preparation containing the four alkaloids of the gland in absolute chemical purity. Extracts from human are as active as extracts from animal glands. [The validity of this claim is by no means generally conceded.—Ed.]—J. K.

(HYPOPHYSIS) Pathogenesis and metabolism in diabetes insipidus with special regard to the chemical analysis of the blood (Zur Frage der Pathogenese und der Stoffwechselvorgänge beim Diebetes insipidus mit besonderer Berucksichtigung der chemischen Untersuchungen des Blutes). Gorke (H.), Arch. f. Verdauungs-Krank. (Berlin), 1920, **26**, 365-398.

Description of four cases with complete examinations. The author comes to these conclusions. Diabetes insipidus is a disease accompanied by polyuria. The polyuria is chiefly caused by a loss of power of concentration of the kidneys for NaCl and other salts. Nitrogen is excreted in normal concentrations. In the blood serum there is a marked hyperchloraemia and an increased depression of the freezing point. When extra doses of NaCl are given the quantity of NaCl in the serum is increased and this increase forms a new stimulant to increase the diuresis. Retention of water in the body after administration of NaCl is possible, but is never very marked. The excretion of extra doses of NaCl is somewhat delayed but rarely takes more than one day. When the quantity of NaCl in the body is reduced the hyperchloraemia and the hyperosmosis become less marked, though a normal freezing point is never reached. The quantity of urine becomes less though always remaining much higher than normal. Fever has but little influence on diuresis. Quantities of urine as in normal persons are never observed. The influence lasts only during a short time. When the fever continues for a long time the diuresis reaches its original height again. When the quantities of fluids given are diminished, the body loses water and thus loses weight, but the quantity of excreted urine is but very little diminished and its concentration remains low. This proves once more the loss of power of concentration of the kidneys. When the quantity of fluid given is diminished, symptoms are observed (tachycardia, thirst, nausea, headache, vertigo), closely resembling uremia. However, these symptoms have no relation whatever to real uremia; they are due only to the loss of water from the tissues. The only way to increase the concentrating power of the kid-

neys is by subcutaneous or intravenous injections of extracts of hypophysis. These injections cause a diminished diuresis, and increased concentration of urine, the hyperchloraemia disappears, the freezing point of the serum becomes normal and the quantity of proteins in the serum is somewhat diminished. These injections do not always cause retention of water. When this happens it is caused by the diminished diuresis. When the diuresis is diminished by injection of extract of hypophysis the body may lose much water by the bowels, the skin and the salivary glands. The diminishing of the diuresis and the increase in concentration are proportional to the quantity of extract injected. Several injections given one soon after the other may cause complete anuria for 9 to 12 hours. When the injections are stopped all symptoms of diabetes insipidus reappear immediately. Three patients with diabetes insipidus showed a marked anhydrosis. In three cases the roentgenogram did not show any sign of hypophyseal disease but as these patients showed amenorrhea the idea is suggested that the hypophysis plays a part in the disease. Two of the patients showed dystrophia adiposogenitalis. This, too, speaks for a hypophyseal influence. Only one patient showed small modifications on the x-ray plate. [The author in his excellent article forgets that Aschner and others have observed atrophy of the generative organs after lesions of the midbrain without any lesion of the hypophysis. There are also many authors who deny any relation between the hypophysis and dystrophia adiposogenitalis.]

—J. K.

(HYPOPHYSIS) The etiology of cystoplastic osteitis (Zur Ätiologie der Ostitis cytoplastica). Hamann (Otto), Med. Klin. (Berlin), 1920, **16,** 63-64.

A case of cystoplastic osteitis, affecting the tibiae of both legs, which yielded to pituitary medication. Hamann concludes that osteitis osteoplastica, leontiasis ossea, and Paget's disease, are due to a hypopituitary condition. The hypopituitary cases all show a regressive condition upon bony growth, leading to cystic bone formation, as in the above mentioned case.—J. H. L.

(HYPOPHYSIS) Studies on proteinogenous amines. IX. Is histamine a normal constituent of the hypophysis cerebri? Hanke (M. T.) & Koessler (K. K.), J. Biol. Chem. (Balt.), 1920, **43,** 557-565.

In contradistinction to the published reports of Abel and Kubota of the finding of 18 mg. of histamine in 1 pound of

dried substance of whole pituitary gland, and their statement that "histamine is the plain-muscle stimulating and depressor constituent of the posterior lobe of the pituitary gland," the authors of this paper conclude, on apparently valid evidence, that the perfectly fresh hypophysis contains no histamine and express the opinion that Abel and Kubota's contention is untenable. They hazard the suggestion that the histamine found by Abel and Kubota in the dried pituitaries may have been the result of the action of putrefactive bacteria on histidine. Exact details are given of the methods of preparation of the various extracts of the fresh pituitary glands, methods which they claim are not sufficiently vigorous to prevent the recovery of histamine for either colorimetric or physiological testing if such be present. However, the methods were sufficiently vigorous to destroy the oxytocic principle, at least in the extracts obtained, for none of them caused contraction of the excised virgin guinea-pig uterus.—F. S. H.

Action of HYPOPHYSEAL extracts on diuresis in dogs and rabbits (Action des extraits hypophysaires sur la diurèse chez les chiens et les lapin). Houssay (B. A.), Galan (J. S.) & Negrette (J.), Compt. rend. Soc. de biol. (Paris), 1920, **83,** 1248-1250.

The posterior lobe of the bovine hypophysis was used in a 20 per cent decoction in saline solution acidified to 0.25 per cent. The experiments were made in three ways: 1.—Action on the diuresis during 24 hours in animals, which fed themselves voluntarily; 2.—Action on animals the food and water of which were measured; 3.—Action on normal and provoked diuresis, collecting the urine at intervals of 1 to 2 hours before and after injection of hypophysis.

It was found in brief that extract of hypophysis provokes an oliguria of short duration in rabbits, with considerable anorexia. In rabbits on a fixed regime there is no effect in 24 hours, although there is an immediate oliguria. In dogs, the extract induces diuresis, which manifests itself during several hours, but does not influence the 24 hour quantity; this quantity may sometimes be diminished. The hypophysis inhibits the diuresis produced by the ingestion of water, probably by retarding its absorption.—T. C. B.

HYPOPHYSIS and scleroderma (Ipofisi e sclerodermia). Izar (Guido), Riforma med. (Napoli), 1920, **36,** 482-486.

A preliminary discussion is given of the multiplicity of factors assigned as causes for scleroderma from which Izar

comes to the conclusion that the theory of a causative endocrine disturbance is the most securely founded. Nevertheless, he cannot agree to a monoglandular conception of the disorder because of the strict interrelationship so often shown in glandular functioning. The case described refers to a girl 7 years old, with well defined scleroderma, giving a positive Cushing reaction and showing an enlarged sella turcica on radioscopic examination. Consequently opotherapy was initiated (pituitary extract and hypophysine). After the sixth injection further development of the sclerodermic lesion was stopped and in less than fifty days the patient was greatly improved. The treatment was continued and seven months after the first treatment the patient was cured.—G. V.

(HYPOPHYSIS) A study of the haemodynamic reaction of the cerebrospinal fluid and hypophyseal extracts. Jacobson (Conrad), Johns Hopkins Hosp. Bull. (Baltimore), 1920, **31**, 185-196.

Briefly stated, the object of the investigation was a study of the physiological effects of intravenous injections of unconcentrated and concentrated spinal fluid, human, bovine and artificial, in contrast with similar injections of hypophyseal extracts, anterior lobe, posterior lobe, pars intermedia and whole gland, in the hope of reaching some definite conclusion regarding the presence or absence of the pituitary secretion in the cerebrospinal fluid.

It was observed that cerebrospinal fluid from human and bovine sources in concentration gives physiological reactions identical with those obtained from the injection of various tissue extracts, effects most probably due to the presence of histamine. There was no definite evidence of the presence of a pressor substance in the cerebrospinal fluid suggestive of any posterior lobe secretion. It seems therefore rather improbable that the pituitary gland, as claimed by Herring, discharges its secretion into the ventricles or into the cerebrospinal fluid. All pituitary gland extracts showed marked variability as far as the responses on intravenous injection are concerned. They all show a depressor effect common to tissue extracts in general. It was noted that: (a) Anterior lobe exhibits depressor effects mainly; (b) Posterior lobe a moderate depressor followed by a specific pressor effect; (c) Pars intermedia has a small depressor, followed by a pressor effect; (d) Whole gland showed a neutralization of the depressor and pressor effect; (e) The posterior lobe secretion, if it is a specific secretion, is most probably produced in the pars intermedia and finds its way into the pars nervosa. The author further observed that

the posterior lobe extract on intravenous injection appeared to have an anti-diuretic effect rather than a diuretic one and that glycosuria was produced by intravenous injection of posterior lobe extract in a number of cases. This glycogenic effect is more marked in the rabbit.—J. F.

(HYPOPHYSIS) Combination of hypophyseal adiposity with poliomyelitis (Kombination von hypophysärer Fettsucht mit Poliomyelitis). Kastan, Deutsche med. Wchnschr. (Berlin), 1920, **46,** 898.

A case is reported, but without any details of special endocrine interest.—J. K.

Correlation between the vasodynamic action of PITUITRIN and that of the ADRENALS (Corrélation entre l'action vasodynamique de la pituitrin et celle des surrénales). Kepinow (L.), Compt. rend. Soc. de biol. (Paris), 1920, **83,** 1134-1135.

The study of the vasodynamic properties of pituitrin led to the question whether this action was dependent on adrenalin circulating in the blood, or on a modification in the sense of an augmentation of the secretion from the adrenals. The answer seemed to lie in the study of the vascular action of pituitrin in the absence of adrenalin. The experiments were done on dogs, the adrenalin being eliminated either by tying the suprarenal vessels, or clipping them with forceps. When the action of the adrenals is thus eliminated, the injection of pituitrin fails to cause a rise in blood pressure, but if the suprarenal veins are released after such an injection, the blood pressure is augmented and presents all the characters of an injection of pituitrin under normal conditions. The indications are that there is a functional interdependence between the vasoconstrictor action of pituitrin and the action of adrenalin. [Hoskins and McPeek reported in 1913 that occlusion of the adrenal circulation in dogs causes no change in the pressor effect of pituitrin. The disparity should be further investigated.—Ed.]—T. C. B.

(HYPOPHYSIS) Pituitary tumor with general edema in two cases of nanism, one of the Paltauf type, the other of the pituitary type. Kraus (W. M.), J. Nerv. & Ment. Dis. (N. Y.), 1917, **45,** 193-213.

These two cases of dwarfism were described together because of certain signs in common. Both showed low basal metabolism, hypoplasia of sexual organs, edema, greatly increased carbohydrate tolerance, lack of body hair, deficent ossification

of epiphyses of large bones and smallness of stature. The skin was dry and wrinkled in both cases and the general appearance was cretinoid. In the first case the sella turcica was shown by x-ray to be greatly enlarged and there were definite eye signs and symptoms of hypophyseal tumor. This man, 48 years of age, was mentally infantile and presented a general appearance resembling in several respects that of an ape. The Paltauf case showed no enlargement of the sella turcica, but at autopsy the posterior lobe of the pituitary body was found to be practically replaced by colloid and the anterior lobe was not made out. The testes were very small and of the infantile type. Development had evidently ceased between the fifth and eighth years. For some months before death this patient showed marked somnolence like that described by Cushing in connection with hypophyseal disease and compared with the phenomenon of hibernation.—I. M.

A case of senile osteomalacia cured by HYPOPHYSIN (Ein mit Hypophysin geheilter Fall von seniler Osteomalazie). Lang (K.), Berl. klin. Wchnschr., 1920, **57**, 658-659.

The patient was a woman of 65 years; her height was 1.27 M. and her weight was 25 Kilos. The whole skeleton showed symptoms of osteomalacia; there was general atrophy of the muscles but no symptoms of tetany. The thyroid was swollen; there were diarrhea and a tremor manifested. The results obtained with phosphorus and cod liver oil and with antithyroidin tablets were meagre. **Adrenin** gave dangerous complications. Following injections of hypophysin (the dose is not given) the patient rapidly improved, though during this treatment the blood pressure became much higher.—J. K.

(HYPOPHYSIS Encephalitis lethargica and pituitrin (Encefalitis letargica y pituitrina). Luengo (E.), Rev. de sanidad militar (Madrid), 1920, **66**, 331.

The author is of the opinion that the hypophysis takes a part in the phenomena of encephalitis lethargica and obtained good results by use of pituitrin in the disorder.—G. M.

(HYPOPHYSIS) Adiposo-genital dystrophy accompanied by epileptic attacks (Distrofia adiposo-genital frusta con ataques epilepticos). Malamud (T.), Prensa Med. Argentina (Buenos Aires), 1920, **7**, —— (June 30th).

Case report of an epileptic of 14 years with adiposity and menstrual difficulties. Improvement followed subcutaneous hypophyseal opotherapy.—B. A. H.

HYPOPHYSEAL and adjacent tumors (Hypophysen—und Hypophysengegendtumoren). Oberndorfer, München. med. Wchnschr., 1920, **67**, 946-948.

Description of some cases.

1. **Rudimentary acromegaly.** A man of 40 died from acute yellow atrophy of the liver. He had two enormous toes. Autopsy showed an enlarged posterior lobe of the hypophysis, the eosinophil cells invading the posterior lobe.

2. **Combination of acromegaly and dystrophia adiposogenitalis.** In this case the patient (a man of 21) died from otitis media. Postmortem showed no trace of hypophyseal tissue. The gland had been replaced by a tumor the size of a hen's egg which compressed the third ventricle.

3. **Dystrophia adiposogenitalis** in a woman of 39. A tumor of the hypophysis the size of a hen's egg was found at autopsy. The tumor had destroyed the sella turcica and had grown into the sphenoidal sinus. There still remained some small residua of the posterior lobe.

4. **Dystrophia adiposogenitalis** in a man of 55. Postmortem: Teratoid of the hypophysis. No hypophyseal tissue left.

5. **Dystrophia adiposogenitalis** in a woman of 63. Postmortem: Hypophysis normal but compressed by a cyst of the infundibulum.

6. **Dystrophia adiposogenitalis** in a woman of 21. Postmortem: Sarcoma of the infundibulum the size of a pigeon's egg.

7. A boy of nearly 6 years with many pigmented birthmarks, headache, paleness and vomiting but no adiposity; exitus. Postmortem: Glioma of the infundibulum.

8. In a patient who died without any typical symptoms, a cancer of the infundibulum compressing the hypophysis was found.—J. K.

Adiposo-genital syndrome with tumor of the HYPOPHYSIS; radio-therapy: regression of the symptoms (Syndrome adiposo-genital chéz un malade porteur d'une tumeur de l'hypophyse: radiotherapie; regression des symptômes). Reverchon, Worms & Rouquier, Bull. et. mem. Soc. med. d. hôp. d. Par. 1920, n. s., **44**, 1084-1085.

A report of physical regression due to pituitary involvement in a young soldier of 27 years. The disturbance probably was due to the effects of an internment caused by the explosion of a shell of high caliber. Radiographic examination having showed an enlarged sella turcica, x-ray applications were made at once for 6 months, with the result that the ocular symptoms

remained stationary, and the evidences of glandular insufficiency gradually passed away.—F. S. H.

Action of the HYPOPHYSIS on renal function (De l'action de l'hypophyse sur les fonctions renales). Romme (M.), Presse méd. (Par.), 1917, **25,** 533.

The author studied the action of various pituitary extracts on the renal function in different subjects. He found that the different gland preparations used gave varying results and considers that this fact accounts for the discrepancies previously reported. In all of his cases posterior lobe material produced a tendency to oliguria with an increase in the concentration of urinary chlorides. He concludes from this that **diabetes insipidus** is due to a reduced activity of the hypophysis. Extracts of the anterior lobe of the hypophysis had no effect on the urine excretion.—I. M.

(HYPOPHYSIS) The effect of pituitary injection on the blood pressure of febrile patients. Schmidt (H. B.), Arch. Int. Med. (Chicago), 1917, **19,** 1059-1061.

The object of the experiment described in this paper was to discern whether or not injections of pituitary extract in therapeutic doses cause a rise in blood pressure in man comparable to that observed in animals. Twenty-seven observations were made on fifteen febrile patients with different diseases. No definite and constant rise was produced in systolic blood pressure after intramuscular injections of the extract, but the diastolic pressure rose in all cases, as much as 15 mm. in some cases. The maximum height was observed after about 30 minutes. Extracts and desiccated gland substance given by mouth had no such effect, even in large doses. Subsequent injections showed the same effects as the primary injection in the same patient.—I. M.

(HYPOPHYSIS) Tumores de la hipofisis. Segura (E. V.), Rev. Asoc. méd. argent. (B. Aires), 1916, **25,** 184.

A brief note to the effect that in four cases the author has obtained remarkable results (visual improvement) by complete excision of the tumors.—R. G. H.

Present knowledge of INTERNAL SECRETIONS. (Gegenwärtige Stand der Lehre von den inneren Sekretion). Asher (L.), Deutsche med. Wchnschr. (Berlin), 1920, **46,** 1028-1030; 1056-1057.

A general review without new data, which fails to give all our present knowledge on the subject. The author is quite sure that the adrenals produce adrenaline and that this has the same action as adrenaline when injected. In the same way dystrophia adiposogenitalis and diabetes insipidus are certainly related to the hypophysis, according to the author. Not a word is said about the highly important work of Leschke, Aschner, Camus, Roussy and others on the function of the midbrain in these diseases.—J. K.

INTERNAL SECRETIONS and tachycardia (Las taquicardias y las secreciones internas). Bonilla (E.), Siglo méd. (Madrid), 1920, **67,** 688-691.

The author studied the influence of the various internal secretions on cardiac rhythm considering that the greater part of the so-called essential tachycardias are due to latent conditions of **hyperthyroidism.** The emotional tachycardias, many examples of which were frequent during the European War, are produced in persons predisposed, by the innate hyperthyroid activity of the emotional act. At times these emotional tachycardias are accompanied by hypertension (Aubertin) which can be explained on a basis of emotional **hyperadrenalism.**—G. M.

(INTERNAL SECRETIONS) Continued fever of sympathetic origin. (La fièvre continue d'origine sympathetique). Cawadias (A.), Ann. de Méd. (Paris), 1920, **7,** 450-455.

A case report is given, as well as a general discussion of those patients in whom there occurs a continuous fever of a mild type which fails to react favorably to any treatment and the diagnosis of which cannot be based on any specifically known cause. Frequently an unstable pulse, emotivity, fatigability and vasomotor troubles are also present. An intensive reaction to adrenaline with negative response to atropine indicates a sympathetic disturbance. No **thyroid** disorder is evident, but occasionally Sergent's white line is present, which may or may not indicate **adrenal** insufficiency as the direct cause of the disturbance. However, since the syndrome described is not due to intoxication, infection or to tuberculosis, it is considered idiopathic and probably has its origin in some disturbance of the internal secretions. The prognosis is favorable and the treatment consists in complete moral, physical and mental repose.—F. S. H.

The influence of INTERNAL SECRETIONS on blood pressure and the formation of bile. Downs (A. W.), Proc. Am. Physiol. Soc., Am. J. Physiol. (Balt.), 1920, **51,** 193-194.

Correction of citation, Endocrin., **4,** 470. The article referred to was afterwards published in full in Am. J. Physiol., 1920, **52,** 498-507. For data see abstract of this latter article.

(INTERNAL SECRETIONS) Studies on the anatomical changes which accompany certain growth disorders of the human body. Keith (A.), J. Anat. (Lond.), 1920, **54,** 101-115.

The name "diaphysial aclasis" is suggested for the disease commonly known to clinicians as multiple exostoses. Because of its relation to achondroplasia it is suspected that the disorder may be due to a disturbance of some of the endocrine glands—most likely of the **thyroid.**—W. J. A.

The INTERNAL SECRETIONS. Scott (T. B.), Practitioner (Lond.), 1917, **99,** 474-481.

The writer discusses the rapidly increasing knowledge of the internal secretions and their therapeutic and pathological significance. He deals with Graves' disease as a pluriglandular disturbance, elaborating on the interrelationship existing between the activity of the **thyroid** and the **adrenals** and between the former and the **parathyroids.** He recommends parathyroid extract in the treatment of acute Graves' disease on the assumption that it normally acts as a balance against overactivity of the thyroid. In cases of the disease with low vascular tension adrenin or suprarenal extract is employed on the ground that its pressor activity is in abeyance in the disease when the depressor action of the thyroid secretion is excessive. In cases in which nerve disturbance is noticeable he uses parathyroid and suprarenal preparations with the manometer as a guide. He expresses great faith in the use of parathyroid for the relief of paralysis agitans, citing examples of its having been employed repeatedly with beneficial results. **Pituitary** extract is claimed to have had undoubted virtue in Graves' disease in his hands. Cases are cited to show its value as a restorer of power in the feebleness of old age.—I. M.

(MAMMA) Epitelio-sarcome de la glande mammarie. Bergeret & Botelho, Gynec. et obst. rev. (Paris), 1920, **1,** 139-147.

Of no endocrine interest.—F. S. H.

(MAMMA) Prolonged mammary secretion. Curettage. Cure (Sécrétion mammaire prolongée. Curettage. Guérison). Hamant (M.), Bull. soc. obst. et gynec. (Paris), 1920, **9**, 164-168; see also Gynec. et obst. rev. (Paris), 1920, **1**, 395-396.

A young woman of 23 years gave birth to a child which she nursed for nearly a year. Although the child was weaned at this time the milk flow continued notwithstanding the application of the usual means to cause it to cease. This condition having continued for two years and more the woman sought medical assistance and the author being of the opinion that a relation exists between the function of lactation and the placenta, considered that the prolonged flow of milk might be due to the intra-uterine retention of some placental fragments from the conception of 2 years previously. He consequently advised a curettage. The advice was accepted and the flow of milk began to diminish 4 or 5 days after the operation and 2 weeks later had entirely stopped. Nevertheless, H. was unable to find any placental cells in the detritus of the curettage. Three months after the operation the patient was relieved of a tubal pregnancy evident on abdominal palpation. No milk flow occurred after this second surgical interference. As an explanation for the result obtained from the curettage H. considers the possibility of placental residues already alluded to as maintaining a constant uterine reflex irritation. He does not look favorably upon an explanation based on psychic factors because the flow of milk did not stop quickly enough. In the discussion M. M. Remy and Froelich dissent from Hamant's explanation.

—F. S. H.

Clinical pathology of the MIDBRAIN (Zur klinischen Pathologie des Zwischenhirns). Leschke (E.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 959-961; 996-997.

The author denies the existence of a relation between the hypophysis and diabetes insipidus on the ground that extirpation of the hypophysis in animals never gives rise to polyuria when the midbrain is not touched during the operation. Extirpation of the lobus posterior produces no symptoms at all; extirpation of the anterior lobe gives rise to hypophyseal cachexia. Likewise, when pathological processes destroy the hypophysis without affecting the midbrain polyuria is never observed, only cachexia, when the anterior lobe is involved. On the other hand, it is possible to produce polyuria by piqure behind the infundibulum in the tuber cinereum of the midbrain. There are many cases known (bullet wounds, brain tumors, gummata, tubercles of the infundibulum, tumors of the

pineal, hemorrhagic insults of the midbrain, and internal hydrocephalus) in which, without any lesion of the hypophysis, diabetes insipidus has occurred through changes in the midbrain. Not only is there a close relationship between the midbrain and diabetes insipidus, but also diabetes mellitus may be closely related to diseases of this part of the brain. The fact that extirpation or diseases of the whole or part of the hypophysis are never followed by glycosuria is an argument against the existence of hypophyseal diabetes. On the other hand, diseases of the midbrain may cause diabetes. Thus may be explained the diabetes that is seen in syphilitic meningitis. This may be expected, for there is a close relation between diabetes insipidus and diabetes mellitus. The author found that in diabetes mellitus with polyuria the kidneys had depressed concentration power. It is the same with diabetes insipidus. In two cases of diabetes mellitus the author found microscopic changes in the cells of the hypothalamus between the corpora mamillaria and the infundibulum. In a third case, however, no changes were found. The midbrain may be the seat of the cause of diabetes mellitus, but it certainly is not the only one.

Dystrophia adiposogenitalis has no dependence upon conditions in the hypophysis. Out of 41 cases the gland was found perfectly normal in 18; in the other cases the hypophyseal tissue was as often increased as diminished. On the other hand, in all cases of dystrophia there are changes in the midbrain. When in the course of experimentation the midbrain is wounded, the animals develop atrophy of the generative organs (Aschner). Adiposity, however, is not always observed. Dystrophia adiposogenitalis may be combined with other midbrain symptoms, as polyuria, subnormal temperature, etc. Other symptoms, due to pathological changes in the midbrain, are: disturbed heat regulation, disturbed pupil reactions, and changes in the sweat and vasomotor reactions.—J. K.

Oxycephaly and NANISM (Oxycephalie et nanism). Isola (A.), Butler (C.), & Mussio-Fournier (J. C.). Bull. et mem. Soc. méd. d. hôp. d. Par., 1920, **44**, 1122-1128.

Anthropometric and clinical study of a curious case of dwarfish, which is diagnosed as oxycephaly and not infantilism because the latter is eliminated by the occurrence of menstruation and the development of the secondary sexual characteristics. Nevertheless an endocrine disturbance of undetermined nature is considered as a possibility.—F. S. H.

Abortive forms of OSTEOMALACIA (Ueber Abortivformen der alimentären Osteomalazie). Koch, München. med. Wchnschr., 1920, **67**, 883.

Of no endocrine interest.—J. K.

Rickets and OSTEOMALACIA. (Rachitis und Osteomalazie). Lehnerdt, Ztschr. f. ärzt. Fortbildung (Jena), 1920, **17**, 433-437; 460-466; 489-498.

Of no endocrine interest.—J. K.

On the postnatal development of the OVARY (albino rat), with especial reference to the number of ova. Arai (H.), Am. J. Anat. (Phila.), 1920, **27**, 405-462.

A careful quantitative study of the number of ova and corpora lutea at all ages from birth to 947 days has been made in the albino rat. Not primarily of endocrine interest.

—W. J. A.

(OVARY) Precocious menstruation with hypergenitalism (Menstruatio praecox mit hypergenitalismus). Lebhardt, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 875.

A very brief case report of a girl in whom regular menstruation appeared at 11. At operation a malignant tumor of the ovary was found and removed. No other details are given.

—J. K.

(OVARY) Contribution to the knowledge of normal and pathological OVULATION and the related uterine processes (Beiträge zur Lehre von der normalen und krankhaften Ovulation und der mit ihr in Beziehung gebrachten Vorgänge am Uterus). Meyer (R.), Arch. f. Gynäk. (Berlin), 1920, **113**, 258-315.

An extensive discussion of ovulation presenting but meagre experimental data. The course of ovulation is defined as consisting of ripening of the ovum and the independent follicular luteinization, together with the functional preparation of the uterine mucosa. The death of the egg cell is said to follow that of the follicle or its previously delimited **corpus luteum.** The final step is the death of the mucosa (Schleimhauttod). According to this conception menstruation is the expression of the failure of the natural processes which result from fertilization and hence the "rule" is the pathological exception. M. considers that the survival of an ovum past menstruation

is impossible. The clearing up of the chemical processes in the functionally prepared and functioning uterine mucosa can only be accomplished when recognition is paid to the fact that the pregravid phenomena are to be sharply differentiated from menstruation considered as a functional death, since it should rather be looked on as a functional failure. One should not speak of a menstrual cycle and premenstrual uterine conditions, since the mucosa, because of the shrunken span of life of the unfertilized ovum, and because of a certain stage of development of the next egg of 3 to 4 weeks duration, will be renewed to a functional pre-gravid state. There is no menstrual cycle, but only a mensual ovulation cycle, the consequence of the failure of domestication. This cycle lasts from the death of one egg to that of another.—F. S. H.

(OVARY) Relation of hyperplasia of endometrium to so-called functional uterine bleeding. Novak (E.), J. Am. M. Ass. (Chicago), 1920, **75**, 292-297.

Since functional uterine bleeding, occurring at the menopause or near the time of puberty, is very frequently accompanied by an endometrial hyperplasia, and since currettage fails to bring a permanent cessation of the menorrhagia, Novak believes that the endometrial changes causing functional bleeding are mere local manifestation of the endocrine disturbance of the ovary. The remarkable cyclic changes of the uterine mucosa which are associated with normal menstruation are directly due to the internal secretory activity of the ovary; hence, if the ovarian secretions are disordered, he assumes that the endometrial response will be abnormal and, conversely, in functional uterine hemorrhage from the hyperplastic endometrium the ovarian secretions are presumably either primarily or secondarily at fault.—F. C. P.

Cancer of the OVARY involving the sigmoid flexure. Truesdale (Philemon E.), Ann. Surg. (Phila.), 1920, **72**, 218-223.

A case report.—J. F.

(OVARY) The ripe human graafian follicle together with some suggestions as to its mode of rupture. Thompson (A.), J. Anat. (Lond.), 1919, **54**, 1-40.

A detailed morphological study is given in which the author is inclined to minimize the influence of the accumulation of liquor folliculi in bringing about the rupture of the follicle, which he considers to be produced by the vascular and nervous disturbances of menstruation or coitus.—W. J. A.

(PANCREAS ADRENALS) A case of endogenous adiposity. (Ein Fall von endogener Fettsucht). Arnold, München. med. Wchnschr., 1920, **67**, 945.

Demonstration of a girl of 13 who had endogenous adiposity since she was two years old. The heart was large and there were manifested status thymolymphaticus and alimentary glucosuria. The weight was 180 pounds. The author is of the opinion that in this case "the adrenal system dominates the pancreas".—J. K.

Degenerative changes in the PANCREAS during gestation (Transformation dégénérative du pancréas pendant la grossesse). Aron (M.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1122-1125.

Chiefly of histological interest. Changes in the peripheral lobules of the pancreas of a pregnant bat are described and hypotheses as to the cause discussed.—T. C. B.

(PANCREAS) Hematic formation in the islands of Langerhans of the embryonic pancreas (Hématiformation dans l'ilôts de Langerhans du pancréas embryonnaire). Aron (M.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1119-1122.

Of histological interest.—T. C. B.

(PANCREAS) The behavior of the pancreas in diabetes in larger children; also studies on the normal structure of the gland at these ages (Das Verhalten der Pankreas beim Diabetes gröszerer Kinder, sowie Untersuchungen über den normalen Bau der Drüse in diesem Alter). Heiberg (K. A.), Arch. f. Kinderh. (Stuttgart), 1916, **65**, 388-391.

Heiberg counted the number of Islands of Langerhans in 50 cmm. of pancreatic tissue and determined the average number in a series of 15 normal children and of 8 diabetics of similar age, 7-18 years. Of the normal children 7 had 76-150 islands per 50 cmm. and 8 had over 150. Of the 8 diabetics only one had over 75 islands per 50 cmm. Heiberg emphasizes the need for the study of the pancreas and the islands, to be placed on a quantitative basis. (Set also Hammar, Endocrin., **4**, 37-46.)
—C. H. G.

(PANCREAS) Fat digestion and diagnosis of pancreatic insufficiency (La digestion des graisses et le diagnostic de l'insuffisance pancréatique). Labbé (M.), & Labbé (H.), Ann. de Méd. (Paris), 1920, **7**, 424-435.

Not of endocrine interest.—F. S. H.

(PANCREAS) Two cases of pancreatitis (acute and chronic) [Deux cas de pancreatite (aigue et chronique)]. Phêlip (J. A.), Arch. d. Méd. d. Enf. (Paris), 1920, **23**, 357.

The author reports a case of acute pancreatitis in a child of seven and one of chronic pancreatitis in a child of ten. In the latter there was also an associated cystic dilatation of the gall bladder. Both cases are of surgical interest only.

—C. H. G.

PANCREAS and its diseases (Over pancreas en pancreasziekten). Vermast (P. F.), Tijdschr. v. Diergenessk. (Utrecht), 1920, **47**, 232-246.

A general review, of no endocrine interest.—J. K.

(PARATHYROIDS) Anatomical and pathological studies of the parathyroids of 64 insane patients (Étude anatomo-pathclogique des parathyroïdes de 64 aliénés). Laignel-Lavastine & Duhem (P.), Ann. de méd. (Paris), 1920, **7**, 409-425.

Contrary to general opinion, the authors were unable to establish the consistent presence of 4 parathyroids in the human subjects studied. Out of the 64 persons examined but 11 had 4 of these glands; in 18 cases 3 were present; in 15 cases 2; in 17 but one was found, and in 3 no parathyroid tissue was demonstrable.

The cells of the gland acini have been designated as the principal cells and the so-called "secondary cells" have been renamed the eosinophil cells because of their particular affinity for eosin. Two types of glandular parenchyma are also described, the one consisting largely of acinar cells and called the acinal type, the other, because of its indefiniteness, is designated as the disperse or diffuse type. Differences in number, form and structure of the parathyroids are found to occur in different subjects and in those of same person.

In senile dementia and a third of the observed cases of general paresis, there was evident a transformation of a more or less large part of the glands to the eosinophile type, which was usually accompanied by a vascular congestion. Fat infiltration of various degrees of intensity was evident in 63 of the cases. A slight increase of connective tissue was frequently noted, although abundant sclerosis was markedly rare. Colloid was found in 26 subjects and occurred as intra-acinal drops more or less abundant.—F. S. H.

On the PARATHYREOID duct of Pepere and its relation to the postbranchial body. Robertson (M.), J. Anat. (Lond.), 1920, **54**, 166-169.

A cyst- or duct-like epithelial structure is described in relation to the thyroid, parathyroid and thumus glands of cats and dogs. In the thymus it is said to give rise to the corpuscles of Hassall by a process of budding.—W. J. A.

(PARATHYROIDS) The cause of Trousseau's symptom in tetany (Zur Kenntnis des Trousseauschen Phänomens bei der Tetanie). Schäffer (H.), Deutsche med. Wchnschr. (Berlin), 1920, **46,** 1073-1075.

Of no immediate endocrine interest.—J. K.

(PARATHYROID) The phosphate and calcium content of serum in the condition of guanidine tetany. Watanabe (C. K.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1918, **15,** 143-145.

The aim of the experiments reported was to study the phosphate and calcium changes in the blood in guanidine tetany for comparison with those occurring in parathyroid tetany. Other workers had previously shown that the lack of parathyroid is accompanied by increased elimination of ammonia, decreased acid excretion and lowering of the hydrogen ion concentration like that following administration of guanidine hydrochloride. Parathyroidectomy causes a marked decrease in the elimination of phosphates in the urine with retention in the blood and also a decrease in the calcium of the tissues. Guanidine nitrogen is increased in parathyroid tetany. Therefore, it was hoped to determine whether the increase in guanidine is the only cause of this phenomenon or whether other factors are involved in the production of parathyroid tetany. Marriott and Howland's methods were employed. Rabbits were given sublethal doses of guanidine hydrochloride subcutaneously and blood samples were taken just before and again 10 to 48 hours after the injection. The phosphate content of the blood was markedly increased but the reduction of calcium was doubtful. No final conclusion as to the main question was reached.—I. M.

The Vineland experience with PINEAL gland extract. Wagner (H. P.), J. Am. M. Ass. (Chicago), 1917, **68,** 1340-1341.

The author briefly reviews the experiments carried out at Vineland in which twenty-seven mentally deficient children were fed a preparation of pineal gland over a considerable period of time to determine if this gland has some active principle, lack of which might be associated with the retarded mental development. While the results were mildly suggestive of a positive reaction, on the whole the findings were little dif-

ferent from those in the control group and the author concludes that the substance of the pineal gland is entirely inert.
—I. M.

On the PINEAL region in human embryos. Warren (J.), Anat. Rec. (Phila.), 1917, **11**, 428-429.

Attention is called to three special features in the development of the pineal region in the human embryo. The first feature pointed out pertains to the primary arches in the roof of the forebrain. These are clearly differentiated in an embryo of 10 mm. and are more fully developed in one of 15 mm. The anlage of the paraphysis is marked by a slight thickening in the paraphyseal arch. The pars intercalaris forms an arch of relatively great length as compared with its appearance in lower vertebrates. No trace of the paraphysis could be found in embryos of from 17 to 22 mm., although its anlage was observed in one 15 mm. embryo and two 16 mm. embryos, as well as in several of from 23 to 44 mm. The paraphyseal arch was seen in all embryos studied. The third point of interest refers to the post-velar arch. A striking feature found in many human embryos is a complicated prolongation of the anterior end of this arch just behind the vellum. As the outgrowth becomes more complicated, tubules are given off which may become detached and appear as blind vesicles buried in the midst of this tubular formation.—I. M.

PLURIGLANDULAR SYNDROME accompanying DIABETES INSIPIDUS; efficacy of hypophyseal opotherapy for the polyuria (Syndrome pluriglandulaire ave diabète insipide: efficacité de l'opotherapie hypophysaire sur la polyurie). Crouzon & Bouttier, Bull. et mem. Soc. méd. h. hôp. d. Par., 1920, **44**, 1114-1121.

A report of a case presenting the two fundamental symptoms of amenorrhea persisting for 3.5 years and a diffuse adiposity of simultaneous onset. Other symptoms were polydipsia, polyuria, polyphagia, apathy, tendency to drowsiness, and evident regression of the psychic faculties, temporal hemianopsia of the right visual field, partial paralysis of the right oculomotor nerve, Argyll-Robertson pupil, and, finally, arterial hypotension and thermic instability. Certain of the symptoms indicated the possibility of a **thyroid** disturbance, the whole giving a picture of probable pluriglandular disorder with a certainty of a **hypophyseal** or juxta-hypophyseal lesion. The only treatment given was the daily injection of extract of the posterior lobe of the hypophysis, equivalent to 0.05 gm. of the dry

powder; other medication contemplated was prevented because of removal of patient from hospital. As a consequence of the administration of the extract the polyuria was markedly relieved.—F. S. H.

(PROSTATE) Enlargement of MAMMARY GLAND after prostatectomy (Vergrösserung der Brustdrüse nach Prostatektomie). Kondoléon (E.), Zentralbl. f. Chir. (Leipzig), 1920, **47**, 1098.

In a man of 70 prostatectomy was carried out. After some weeks it was observed that the right mamma was swollen. The swelling disappeared later on without treatment. In another case (also a man of 70) both mammae became larger after prostatectomy, but the swelling did not disappear.—J. K.

PROSTATECTOMY. Bugbee (H. G.), Boston M. & S. J., 1920, **183**, 41-47.

Refers to previous works which deal with the results of castration and vasectomy upon the hypertrophied prostate. Nothing new of endocrine interest.—H. W.

(STATUS THYMICOLYMPHATICUS), Idiopathic hypertrophy of the heart in young children. Howland (J.), Contributions to medical and biological research dedicated to Sir William Osler. Hoeber (New York), 1919, **1**, 582.

Howland reports five cases of idiopathic hypertrophy of the heart in children ranging in age from 10 to 48 months. Four of these were diagnosed clinically and one was followed over a period of three months before exitus. No anatomical cause for the condition was found. The thymus varied in weight from 8 to 22 gm. in the different cases, but Howland points out the extreme normal variability in the weight of the thymus and the absence of cardiac hypertrophy in the usual clinical cases of status thymicolymphaticus. Microscopically the heart muscle in these cases showed no essential change from the normal. In a critical review of the literature Howland is content to re-emphasize the obscurity of this condition. (See Riesenfeld, Abst. in this issue).—C. H. G.

STATUS THYMICOLYMPHATICUS, Primary cardiac hypertrophy in early childhood and its relation to—(Über primäre Herzhypertrophie im frühen Kindesalter und ihre Beziehung zum Status thymico-lymphaticus). Riesenfeld (A.), Jahrb. f. Kinderh. (Berlin), 1917, **86**, 419.

Riesenfeld reviews the literature on the congenital idiopathic hypertrophy of the heart in detail and gives a general discussion of the earlier hypotheses in regard to the origin of this condition. He reports an additional five cases in infants, ranging from 9 to 18 months old. These cases were all seen in the acute terminal stage of this disease. The clinical diagnosis of the hypertrophy was possible in all cases and in three it was confirmed by roentgenograms. According to the author the only constant factor present in all five cases was a well marked status lymphaticus. Unfortunately the autopsy protocols are all given in abstract and in only one case was the actual weight of the thymus mentioned; it was 14 gm. in an 11 months old boy. In addition to the gross pathological findings microscopic examination showed diffuse lymphocytic infiltration of the heart muscle. Riesenfeld feels that the hypertrophy may in part be due to the mechanical effect of the enlarged thymus, but that the casual factors more probably are to be found in the endocrine disturbances associated with the status thymicolyphaticus. In this connection he remarks upon the hypoplasia of the adrenal medulla found in one of his cases.—C. H. G.

(TESTES) The man young at fifty. Periodicities, cycles of energizing organic rhythyms. II. Critical epochs in the reproductive cycles. Taylor (J. M.), Med. Times (N. Y.), 1920, **48**, 235-238.

An interesting article in which the author attempts to show that men have a more or less well defined sexual cycle and that they demonstrate phenomena which are the equivalent of the climacteric period in women. New data to support such a view are not offered.—H. W.

Experiences in TESTICLE transplantation. Stanley (L. L.), Calif. State J. M., (San Fran.), 1920, **18**, 251-253.

The author reports the results of 11 transplants of human testes and 21 of young rams into men. Such transplants seemed to have an invigorating effect upon the recipients, sexually and psychically. The implant (entire testes) does not live but becomes necrotic; however, in the process of necrosis certain unknown potent substances are probably released into the system. The glands of rams seem to be as effective as those of man. These glands may be kept for a week or longer by immersion in vaseline and freezing. Slices of testes placed in the abdominal cavity do not show the same tendency to slough as do entire glands when placed in the scrotum.—H. W.

TESTICLE transplantation. Stanley (L. L.) & Kelker, (G. D.), J. Am. M. Ass. (Chicago), 1920, **75**, 1501-1503.

These authors report the result of eleven cases of testicle transplantation. In five cases only one testicle was implanted into the scrotum; in six cases two testicles were implanted. In one case, the testicle of a ram transplanted to man, began to slough in sixteen days. In three cases, one-half of the ram's testicle began to slough in seven days. In three cases human material was placed in a bed made in scrotal tissue, and in seven cases the testicle was grafted on the atrophied testicle of the recipient. In the case of one patient 25 years of age, who was dull mentally and inactive physically, mental acuteness improved and he became a better laborer after having a double graft from a man 27 years of age. In a case of a man 72 years of age, who had never had normal sex impulses, after a double graft from a 19 year old boy, improvement physically, a lower pitched voice and more mental activity resulted. Judging from their limited number of cases, the authors concluded that the transplantation of the human testicle has a decided beneficial effect on the well-being of a patient. They do not believe that the transplant lives. Their experience shows that the beneficial results probably last more than one year.—F. C. P.

The behavior of the interstitial cells of the TESTIS toward vital dyes. Addison (W. H. F.) & Thorington (J. M.), Anat. Rec. (Phila.), 1916, **11**, 318-319.

Vital staining with trypan blue reveals two types of cells in the intertubular structure of the testis. One type is elongated in the form of fibroblasts, while the other is rounded or polyhedral in shape. Both types, according to the definition of Evans, are to be considered as macrophages and are not, as Goldmann interpreted them to be, identical with the interstitial cells of Leydig which represent the testicular organ of internal secretion. The vital staining with counterstain makes it possible definitely to differentiate between the interstitial cells and the macrophages.—I. M.

(TESTIS) Hypertrophy of the interstitial tissue of the testicle in man. Goddard (T. R.), J. Anat. (Lond.), 1920, **54**, 173-176.

Examination of five undescended testicles showed a distinct hypertrophy of the interstial tissue accompanying atrophy of the seminal epithelium. The testis of a man of 78 years also showed hypertrophy of the interstitial tissue.—W. J. A.

Enlarged THYMUS GLAND in infancy and its treatment by radium. Brayton (H. W.) & Heubelin (A. C.), Bost. M. & S. J., 1919, **181**, 740-743.

The symptoms of enlarged thymus gland are divided by the authors into the two classes, general and local. The first group is characterized by faulty endocrine function, such as flabbiness of the tissues, lack of resistance to acute infections, liability to frequent convulsions, eczema and mental retardation. The local symptoms on the other hand are referable entirely to the mechanical effects of pressure on adjacent vital structures enclosed with the organ in the upper part of the rigid chest cavity. These are laryngeal spasm, heart shock, pulmonary engorgement and tracheal compression, with cough, dyspnea and cyanosis. There may be no general symptoms in a given case, but, where thymic enlargement is suspected, the diagnosis is made from the history of pressure symptoms, substernal dullness on percussion and the x-ray shadow. While it has been demonstrated by Friedlander and others that properly standardized x-ray therapy is successful in a high percentages of these cases, the authors were the first to employ radium in this connection. Every one of 34 cases treated by radium was promptly cured by the first exposure, as shown by disappearance of symptoms and by x-ray findings at varying intervals after treatment. The technique used is as follows: 100 milligrams of radium element in its 0.3 mm. silver capsule is wrapped in sufficient gauze to hold it at a distance of about one-half inch from the skin surface. Four marks are then made in the form of a rectangle over the area of thymic enlargement. The radium is applied over each mark in succession for a period of two hours, making a total dose of 800 milligram hours. This mode of treatment has several advantages over x-ray therapy. One application only is required for cure; complicated apparatus, skilled operators and the bad psychical effects of the x-ray technique are avoided.—I. M.

(THYMUS) Microscopic analysis of the thymus in 14 cases of so-called thymus deaths (Mikroscopische Analyse der Thymus in 14 Fälle sogenannten Thymustodes). Hammar (J. A.), Ztschr. f. Kinderh. (Berlin), 1916, **13**, 152-217.

See Endocrinology, 1917, **1**, 88.

(THYMUS) Hirschsprung's syndrome and diffuse spinal gliosis; Bartel's status hypoplasticus (Sindrome de Hirschprung, gliosi spinali diffusa e stato ipoplastico). Pende (N.) & Fici (V.), Riforma Med. (Napoli), 1920, **36**, 504-597.

A case history of the simultaneous occurrence of the 3 dis orders named in the title. The authors attempt to coalesce the varied syndromes under one caption, i. e., status hypoplasticus, basing their conception on the wider meaning given by Bartel to the status lymphaticus as an indication of organic immaturity. The gliosis as found at the post mortem examination is explained as a congenital abnormality of the spinal cord which proceeds after birth with proliferation of the epithelium of the ependymal canal and of the glial tissue. The megalocolon, though it brought the patient to death because of an acute ileus at the age of 36, can be easily classified as a congenital abnormality, as it would belong to those abnormal developments of the gastro-enteric canal, such as diverticula, congenital atresia, abnormal length of the intestine, etc., forms found very often accompanying status thymus-lymphaticus and status hypoplasticus.—G. V.

THYMUS function in growth (La funcion del timo y el crecimiento). Sans (A. Lorente), Aragon med. (Zaragoza), 1920, **38,** 241-243.

A general review without original points of view.—G. M.

(THYMUS THYROID) Ligation of the superior pole of the thymus in operating for goitre. Stewart (L. F.), Penn. M. J. (Athens), 1917, **20,** 751-755.

The opinions of surgeons concerning abnormalities in the thymus as a factor in exophthalmic goitre are summed up and the conclusion is drawn that, while in some cases both thymus and thyroid are responsible, there is no satisfactory proof that the thymus is ever the sole factor. From ten special dissections it was found that the inferior thyroid artery gives an important branch to the superior lobes of the thymus in the majority of cases. The author believes that the ordinary ligation of the inferior thyroid artery near the gland leaves an increased blood supply to the upper pole of the thymus, thereby causing this portion of the gland to become congested and enlarged to the great detriment of the patient. He therefore, dissects into the carotid sheath and ligates the inferior artery behind it in order to include the thymus branch in the ligation and thereby cut off the blood supply from two toxic glands at once.—I. M.

Experiments with feeding THYMUS GLAND to frog larvae. Swingle (W. W.), Biol. Bull (Woods Hole), 1917, **33,** 117-133.

The experiments recorded were undertaken in an attempt to repeat some of the work of Gudernatsch who found that

feeding fresh thymus gland to tadpoles stimulates the growth processes and inhibits the onset of metamorphosis. A rather extensive review of the literature is given.

In one set of experiments fresh gland was fed and in a second series thymus powder was given. The control animals were fed beef liver in equivalent quantities. Rana pipiens, R. catesbiana and one undetermined species were employed in the study. The author's results are at varianee with those of Gudernatsch in that no acceleration of the growth processes was produced by feeding either fresh or powdered thymus. Some of the observations recorded indicate that thymus feeding may have a slight inhibitory effect upon limb development but even this may be only apparent since the normal variability of frog larvae in this respect is so great. The author suggests the possibility that the digestive enzymes may destroy the growth-accelerating principle of the gland so that feeding is not the best test of the gland's activity.—I. M.

Does the THYMUS GLAND of mammals when given as food to amphibians exert any specific influence upon the organism? Uhlenhuth (E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1917, **15**, 37-40.

A report is presented of experiments undertaken to answer this question. Several species of amphibians (A. tigrinum, A. opacum and A. punctatum) were employed in the study, the individuals being divided into two groups, one of which received an exclusive diet of mammalian thymus gland while the other or control series were given the regular diet of earthworms. It was shown that the thymus diet exerts no specific growth promoting influence on the salamander larvae so fed. The apparent faster growth of amphibians following thymus feeding, reported by other workers, is explained in the present communication as being due to the greater quantity of food contained in a given weight of thymus gland as compared with that in an equal weight of earth worms. The earth worm contains a great deal of indigestible matter, i. e., soil, cuticle, etc. As regards the effect of thymus on metamorphosis the different species of the same genus vary greatly; e. g., A. tigrinum showed no acceleration whereas in A. opacum it was greatly accelerated. Individuals of the same species also differ in this respect as in a few cases of A. opacum, metamorphosis was unusually late. Low temperature was probably a factor in the cases noted. In these experiments it was noted that larvae receiving an exclusive diet of thymus showed convulsions which continued until about the time when the **parathyroids** first appear.—I. M.

A case of THYROID insufficiency (Un caso de insuficienca tiroidea). Abasanez (E.), An. de la Acad. med-quir. de Madrid. 1919, **6,** 367-369.

Case report of no especial interest.—G. M.

(THYROID) Case of urticaria of eight years duration with hyperthyroidism. Barber (H. W.), Guy's Hosp. Gaz. (Lond.), 1920, **34,** 115-118.

This interesting case of hyperthyroidism associated with urticaria arose as a result of chronic tonsillar infection. Removal of the tonsils brought about improvement.—J. H. L.

(THYROID) An emergency technic for thyroidectomy. Bartlett (W.), J. Am. M. Ass. (Chicago), 1920, **75,** 169-175.

Of technical surgical interest.—F. C. P.

(THYROID) Acute thyroiditis. Beilby (G. E.), N. York M. J., 1919, **109,** 876; Albany M. Ann., 1919, **40,** 173.

Data published elsewhere. See Endocrin. **3,** 409.

(THYROID) Surgical treatment of hyperthyroidism—relation existing between the amount of gland removed and the permancy of relief. Beilby (G. E.), N. Y. State J. M. (N. Y.), 1920, **20,** 230-231.

If sufficient of the thyroid gland is removed the toxic symptoms of hyperthyroidism disappear and the patient has permanent relief. To accomplish this result the author removes from five-sixths to nine-tenths of the gland. The removal of a single lobe will often give relief but it will not cure. A portion of a lobe, the blood supply of which is not disturbed, may later hypertrophy and produce symptoms. For these reasons the glandular tissue left should be scattered and small.—H. W.

(THYROID) The treatment of hyperthyroidism (Contribucion al estudio del tratamiento de los estados hipertiroideos). Bonilla (E.), Siglo méd. (Madrid), 1919, **66,** 105-108.

A study of conditions of hyperthyroidism is here reported based on the opinion that the greater number of such cases are susceptible to medical treatment. An alimentary regimen is used consisting of carbohydrates (save where glucosuria is present) and fats. Both physical and psychic rest is prescribed, while antithyroid serum is given and in addition **ovarian** substance to the women, since great importance is attached to

gonadal insufficiency in the production of the syndrome. Physicians are warned against the use of iodine in these disorders.
—G. M.

(THYROID) Some pitfalls in the diagnosis of exophthalmic goiter. Bram (Israel), Ann. med. (N. Y.), 1919, **n. s. 25,** 266-268.

A review containing no new data.—J. H. L.

(THYROID) Delayed hereditary lues (Lues hereditaria tardia: Endocrinopatias. II. Tiroides). Castex (M. R.), & Waldorp (C. P.), Prensa Med. Argentina (Buenos Aires), 1920, **7,** ——, (July).

The stigmata of hereditary syphilis are in large part due to thyroid dystrophy. The nasal hydrorrhea often has as its cause a hypo- or dys-thyroidism. Mongolism is a dystrophy of endocrine origin produced by syphilis.—B. A. H.

(THYROID) Development of myxedema after treatment of Graves' disease with x-rays (Ueber die Unwandlung des Morbus Basedowii in Myxoedem durch die Röntgenbehandlung). Cordua (R.), Mitt. a. d. Grenzgeb. d. Med .u. Chir. (Jena), 1920, **32,** 283-295.

A woman of 38 showed all symptoms of classical Graves' disease. As treatment with rest and drugs had no effect, x-ray treatment was tried. After five or six applications rapid improvement occurred. After some time she complained of loss of hair, dullness and diminished perspiration. Menstruation remained regular. The skin showed the typical symptoms of myxedema. Thyroidin was then given and caused much improvement, without complete cure, however. These cases are very rare; the opposite, myxedema changing into Graves' disease has also been described. This case must certainly be attributed to the x-rays, as in spontaneous cases progress is much slower. It is necessary to be very careful to measure the dose of x-rays with exactness.—J. K.

(THYROID) Practical points in goiter surgery. Cottis (G. W.), N. Y. State J. M. (N. Y.), 1920, **20,** 290-294.

Of surgical interest.—H. W.

(THYROID) Special consideration of the adenoma in relation to exophthalmic goitre. Crile (George W.), Ann. Surg. (Phila.), 1920, **72,** 141-144.

The author makes no differentiation between exophthalmic goitre with hyperplasia and thyrotoxicosis from adenomata. He summarizes the special points in his treatment of these cases. This is based upon a personal experience of 2477 thyroidectomies. The last series since the foregoing plan has been routinely employed consists of 562 thyroidectomies. No case was refused and the mortality rate in cases of exophthalmic goitre was one per cent.—J. F.

(THYROID) Hyperthyroidism and iodides (Mecanismo de la acción terapéutica del yoduro en los estados de hipertiroidismo). Delgado (Honorio F.), Crón. Méd. (Lima, Perü), 1919, **36,** 155.

Excellent results from the use of potassium iodid are claimed by Delgado in certain cases of hyperthyroidism. The mechanism of its action is not clear, he states, but the fact of the efficiency of potassium iodide in his cases was beyond question. In the case reported, the enlargement of the thyroid, tachycardia and exophtalmos had developed with hallucinations and distress, after a period of emotional stress and financial worry. Delgado used psychotherapy and gave daily 4 gm. of potassium iodide, and in two days nearly all the symptoms had disappeared.—J. Nerv. & Ment. Dis., **52,** 34.

(THYROID)—Advantages of local anesthesia in thyroid operations. Eastman (J. R.), J. Am. M. Ass. (Chicago), 1920, **75,** 166-169.

This excellent paper describes in detail the advantages of local anesthesia in operations on the thyroid gland and gives details of the author's method of removal of this gland under local anesthesia.—F. C. P.

(THYROID) Superficial percussion of the apices of the lungs in goiter (Schallverkürzungen über den Lungenspitzen bei bestehender Struma). Elias (H.) & Pick (R.), Wien. klin. Wchnschr., 1920, **33,** 674-676.

The author discusses the problems of differential diagnosis between inflammation of the pulmonary apices and goiter. The article is of technical but not immediate endocrine interest.

—J. K.

Cancer of the THYROID. Eliot, Ann. Surg. (Phila.), 1920, **72,** 381-382.

Eliot presented before the New York Surgical Society a woman, thirty-two years of age, who had been admitted to the hospital in December, 1916, complaining of a lump in her neck about the size of a hen's egg. It was of three years duration and of gradual growth. This had been her sole complaint until five months before admission, when she noticed dyspnoea on walking. Resection of the right half of the thyroid was made without difficulty. Pathological study, however, revealed a true carcinoma of the gland. The symptoms were entirely different from those of malignancy and the author is of the opinion that the carcinoma was a recent development.—J. F.

THYROID dyspepsias (Dispepsias tiroideas). Escudero (P.), Rev. españ. med. y cir. (Barcelona), 1920, —, 355-366.

The author discusses in this extensive and interesting work the conjunction of gastric alterations observed with thyroid processes. In hypothyroidism, as Hernando, Levi and Rothschild and others have noted, hypochylous conditions predominate. According to Escudero the greater part of the hypochylias and functional achylias have such an origin. In hyperthyroidism, on the contrary, there is a tendency toward high gastric values. Marañon has shown the frequency with which hyperchlorhydria accompanies hyperthyroidism. According to Escudero the first symptoms in these disorders are the painful phenomena; then the motor reactions (gastric hypertonicity, pyloric spasm) and, finally, the secretory (hypersecretion). Thyroid opotherapy in cases of the first group and anti-thyroid serum in those of the second are very useful. The article ends with interesting descriptions of 18 clinical histories.—G. M.

(THYROID) Graves' disease and goitre with heart complications (Basedow und Struma mit Herzstörungen). Fahr, München. med. Wchnschr., 1920, **67**, 884.

In 24 cases of Graves' disease or goiter, perivascular and interstitial lymphocytic infiltration of the cardiac muscle was found. In three cases there were only pathological changes of an older date. Status thymolymphaticus or persistent **thymus** was often encountered. Pathological changes in the heart may occur in goiter without symptoms of Graves' disease.—J. K.

(THYROID) Hysteric chorea and hyperthyroidism (Corea histerica e hipertirodismo). Fernandez Sanz, Medicina y libros (Madrid), 1919, **4**, 158-160.

This article refers to the case of a young female who was affected with continuous and diffuse motor alterations distinct

from all tics and systematized choreas. The author considers these alterations as a species of functional psycho-neurotic manifestation. When these attacks occurred there appeared a small lump on the middle lobe of the thyroid. The author supposes that moderate hyperthyroidism is connected with pseudochoreic disturbances.—G. M.

(THYROID) The management of toxic goitre from the surgical point of view. Frazier (Chas. H.), Ann. Surg. (Phila.), 1920, **72,** 155-160.

A brief resumé of the current literature and a discussion of the management of these cases based upon 339 cases with a mortality after resection of about one per cent. The author emphasizes the importance of making a determination of the metabolic rate and the limitations of the x-ray in the treatment of these patients. The author has applied the Goetsch test routinely during the past few months but has found it of little aid. —J. F.

(THYROID) A "tourniquet" operation in toxic and other goitres. Freeman (Leonard), Ann. Surg. (Phila.), 1920, **72,** 161-163.

Of technical interest to surgeons.—J. F.

(THYROID) Tachycardiac neuroses and abortive Graves' disease (Quelques remarques sur les névroses tachycardiques et la maladie de Basedow fruste. Gallavardin (Louis), Arch. d. mal du Cœur (Paris), 1916, **9,** 45-64.

When cases of tachycardia are encountered which are not otherwise accounted for, one should always think of subacute thyroidism. The symptoms of this condition and of "nervous tachycardia" are identical. In both conditions the same variability of heart acceleration is seen, as well as the same type of matutinal tachycardia and the same clinical forms, with the tachycardia intermittent or episodic. The whole picture amounts, in effect, to intense excitability of the sympathetic system, not only the cardio-accelerator fibers, but also the vasoconstrictors with consequent vascular hypertension.—R .G. H.

Recent advances in the diagnosis and treatment of THYROID disease based on the use of the epinephrin hypersensitiveness test. A. The differentation of tuberculosis and hyperthyroidism due to "diffuse aderomatosis." Goetsch (E.), N. Y. State J. M. (N. Y.), 1920, **20,** 282-286.

This same subject is covered in an article by Goetsch which appeared in Endocrin. 1920, **4,** 389-402.—H. W.

(THYROID OVARY) Cure of goitre and cardiac insufficiency by radiation of the ovaries. (Beseitigung einer Struma und Heilung einer Herzinsuffiziens durch Röntgenbestrahlung der Ovarien). Groedel, München. med. Wchnschr., 1920, **67**, 882-883.

A woman of 28 suffered from a large goitre, cardiac insufficiency and a pulsis irregularis perpetuus. When she was 40 she was suffering from a myoma of the uterus and lost enormous quantities of blood. An intensive treatment of the ovaries with x-rays was tried. Not only the goiter disappeared but the cardiac disturbance was also cured. It would be of interest to study the thyroid in women during and after sterilization with x-rays. In cases of myoma of the uterus and hyperfunction of the thyroid, sterilization with x-rays must be warmly recommended. It is necessary exactly to measure the quantity of x-rays used.—J. K.

(THYROID) Hyperplasia of the SALIVARY GLANDS and diseases of the ENDOCRINE ORGANS (Speicheldrüsenhyperplasie und Erkankung endokriner Drüsen). Hämmerli (A.), Deutsch. Arch. f. klin. Med. (Leipzig), 1920, **133**, 111-124.

Diseases of the salivary glands associated with affections of the endocrine organs have been rather frequently described, but this is the first instance reported in which a histological examination was carried out. The author describes the combination indicated, in an insane individual of 50 years. Autopsy showed both parotid and submaxillary glands enlarged and a goitre weighing 1050 grams. The enlargement of the submaxillary glands was due to hypertrophy of the glandular tissue. The **adrenals** were large as was also the **pancreas.** The **testicles** were small and brown.

The combination of hyperplasia of the salivary glands with goitre is not so very rare. Often **status thymolymphaticus** is also present. There may be also found in the literature descriptions of combined disease of the salivary glands and of the gonads or the **hypophysis.** The author thought there may possibly exist a relation between the thyroid and the salivary glands. Therefore, he regularly weighed the thyroid and submaxillary glands at every autopsy performed for some time, and found that their weight is always absolutely parellel. A heavy thyroid is always accompanied by large salivary glands and vice versa. May not the submaxillary glands, therefore, be regarded as endocrine organs? Though many authors have

written on this subject, this question is not yet settled; it is probable that these glands have a certain endocrine function.
—J. K.

(THYROID) Improvements in the surgical treatment of goiter (Ueber Fortschritte in der operativen Behandlung des Kropfleidens). Hartert, München. med. Wchnschr., 1920, **67,** 948.

Of technical interest to surgeons.—J. K.

(THYROID) Successive transplantation of thyroid tissue into the same host. Hesselberg (Cora) & Loeb (L.), J. Med. Research (Boston), 1918, **38,** 33-53.

The results of the successive homoiotransplantation of thyroid tissue into guinea pigs leads the authors to the tentative opinion that while the transplanted thyroid resembles certain tumors in the lymphocytic reaction brought about, there exists a difference in the behavior of the second transplantation in the case of these tumors and of thyroid, in that the latter did not appear to develop a markedly accelerated lymphocytic reaction. The lymphocytic reaction which develops because of the thyroid depends upon the relation of transplant and host, a change in either modifying the result. The transplanted thyroid develops definite structural peculiarities which differ from those of the normal thyroid, e. g., the development of solid strands of acini. The lymphocytic reaction is not prevented by pregnancy, loss of weight, dying state, or greater age. Much of the colloid in the acini is destroyed through phagocytic action, and if fat tissue is transplanted with the thyroid the adjacent acini usually become necrotic.—F. S. H.

The effect of administration of small amounts of THYROID gland on the size and weight of certain organs in the male white rat. Hewitt (J. A.), Quart. J. Exper. Physiol. (Lond.), 1920, **12,** 347-354.

In view of the conflicting results of thyroid feeding on the various organs by Herring and by Hoskins on the one hand, and by Kuriyama on the other, it seemed advisable to investigate the matter further. The work of Kuriyama is reviewed critically. Male rats were used and the change in weight of the organs after feeding 0.1 gm. fresh thyroid per day is given as percentage of the corresponding organs of the standard rats of Donaldson. In general the results of Herring and of Hoskins are confirmed. There is hypertrophy of the heart, liver, spleen, kidneys, **suprarenals,** and possibly the **pituitary.** The thyroid is diminished. There is a tendency for the organs to

resume their normal proportions after resumption of the ordinary diet, the alteration in size becoming less marked according to the length of time elapsed after cessation of thyroid feeding.—T. C. B.

(THYROID) Experimental goiter induced by water from the Cerrillos (Salta) [Goitre expérimental provoqué par l'eau de Cerrillos (Salta)]. Houssay (B. A.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1244.

There is much discussion in South America whether certain waters can produce goiter. Experiments were made at Buenos Aires, with waters from goitrous regions. The water was transported in sterile demijohns and was 3 days in transport. In spite of the unfavorable circumstances, 2 white rats developed goiter after four and a half months of experiment and eighty-two days' ingestion of water from the Cerrillos. The water was mixed with bread and milk. It is suggested that the experiments should be repeated under better conditions.
—T. C. B.

(THYROID) Thyroidectomy in the horse (La thyroïdectomie chez les chevaux). Houssay (B. A.) & Hug (H.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1242-1243.

The experiments were made on 8 horses. Their ages varied between 2 months and 2 years. Three colts died of cachexia 5 or 6 months after the operation. Retardation of growth was very marked in the 6 young animals. Five of the animals developed marked synovial edema. Diphtheria toxin injected in some of the horses provoked a marked edema. There was retardation in the development of the permanent teeth. Nearly all were excessively tranquil and docile in disposition.—T. C. B.

(THYROID) Hyperthyoidism and pseudohysteria (Hipertiroidismo y pseudo histerismo). Juarros (C.), Plus Ultra (Madrid), 1919, **2**, 350-354.

The author remarks upon the frequency with which diagnosis confounds hysteria and hyperthyroidism in women, due, he supposes, to an equivocal conception of the former affection and lack of clinical exploration. In order to avoid this confusion, Juarros insists on the necessity for the presence of a perfectly defined hysterical mentality before diagnosing hysteria, and that symptoms of hyperthyroidism should be sought for in all women apparently suffering from this disorder. In those cases in which the result of the clinical examination is

not characteristic, this author recommends employment by way of proof, of antithyroid medication and laboratory methods such as the determination of the basal metabolism according to Benedict, and the glucose tolerance or alimentary glycosuria test.—E. B.

(THYROID) The result of surgical treatment of exophthalmic goitre. Judd (E. S.), N. Y. State J. M. (N. Y.), 1920, **20,** 287-290.

Subtotal thyroidectomy actually removes changed tissue; as a result the metabolic rate is reduced approximately to normal and the symptoms subside rapidly in a great majority of cases. X-ray and radium treatments modify the severity of the hyperthyroid state, but do not cure the disease. The paper is based upon the results of 100 consecutive goiter cases. Of this number 60 per cent were dismissed cured; 13.5 per cent with marked improvement; 5.5 per cent with slight improvement; 15 per cent died. The average blood pressure before operation was: systolic 145.2, diastolic 75.6. The average pulse rate before operation was 122.6 per minute.—H. W.

(THYROID) Results of operations for adenoma with hyperthyroidism and exophthalmic goitre. Judd (Edward S.), Ann. Surg. (Phila.), 1920, **72,** 145-154.

This study of the operative results in these two diseases of the thyroid is based upon two selected groups of one hundred cases each. One hundred consecutive cases of exophthalmic goitre were chosen from the 1914 series at the Mayo Clinic and one hundred consecutive cases of adenoma with hyperthyroidism from the 1917-18 series. The analysis revealed that 65 per cent of the patients suffering from exophthalmic goitre were free from all evidence of the disease six years after operations, while 15 per cent were dead from all causes. Most of the others were benefited. More than 80 per cent of the patients with adenoma with hyperthyroidism were relieved of their toxic symptoms and a cure obtained by thyroidectomy. It is the opinion of the author that a higher percentage of cures would undoubtedly obtain if the patients were all operated upon before there was any evidence of edema or terminal degeneration.—J. F.

(THYROID) Seven cases of nocturnal shaking of the head (Sieben Fälle von nächtlichem Kopfschütteln). Kalmus, München. med Wchnschr., 1920, **67,** 883.

The above mentioned symptom was observed in a girl of 11 years with symptoms of myxedema. Since by **thyroid** treatment the shaking of the head disappeared it was also tried in 6 other children with complete success.—J. K.

(THYROID) Present status of non-surgical treatment of Graves' disease (Der jetzige Stand der nictoperativen Behandlung der Basedowschen Krankheit). Klewitz (F.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 971-973.

Cases of goitre with symptoms of malignancy, or with compression of the trachea or oesophagus, must always be operated upon, as must also chronic cases or cases in which the goitre shows colloid or cystic degeneration. Internal treatment is indicated in the "formes frustes" and in the acute or subacute cases; also in patients with a complication which will not allow surgical treatment, and in convalescence after operations, though of course in these cases the prognosis is never good. It would be desirable to exclude patients with status thymolymphaticus from operation but it is nearly always impossible to diagnose these cases during life.

Non-operative treatment consists of drugs, physiotherapeutic measures, and diet. Bromides and arsenic are recommended. Sodium phosphate, as recommended by Kocher, in the hands of the author never has given good results. Iodine in extremely small quantities, as recommended by Neiszer, may be tried. From the milk or serum of thyroidectomized animals and from **thymus** or **ovary** preparations not much may be expected. As regards physical methods, electrical treatment with constant currents is recommended, but much better effects are obtained from deep radiation of the thyroid. It is dangerous to submit every patient to this treatment, but the author does not indicate which patients are suitable for it. It is absolutely necessary to choose the quantity of x-rays exactly. In cases of Graves' diseases caused by the **thymus** this gland also may be radiated. These cases may perhaps be recognized by an enlarged shadow of the mediastinum on the Roentgen screen, myasthenic symptoms on electrical stimulation of the muscles, symptoms of vagotonia, very marked lymphocytosis, and a positive Abderhalden test against thymus. Another good physical method is CO_2 baths or indifferent baths. Rest in bed during the first weeks of treatment is necessary. Diets during treatment must be rich in calories. It is not necessary to forbid all meat. Many small meals ought to be given. After this combined treatment exophthalmus and goitre may remain unaltered but the nervous symptoms, the tachycardia, and the loss of weight disappear and the patients are again able to go about their work.—J. K.

(THYROID) Diagnosis and management of intra-thoracic goiters. Lahey (F. H.), J. Am. M. Ass. (Chicago), 1920, **75,** 163-165.

Lahey emphasizes the importance of the x-ray in the diagnosis of intra-thoracic goiters and describes the surgical technique for their removal.—F. C. P.

The histology of tadpoles fed with THYROID. Lim (R. K. S.), Quart. J. Exper. Physiol. (Lond.), 1920, **12,** 303-316.

A brief abstract has already been given (See Endocrin., 1920, **4,** 174). The paper is chiefly concerned with the histology of the organs after thyroid feeding. All the organs appear more adult in character. Metamorphosis is induced and hastened. There is a rapid absorption of the tail, the caudal muscles being disintegrated, partly by phagocytes and partly by autolysis. The alimentary tract is the first to be affected by thyroid treatment, the large thin-walled larval type being replaced by a thick-walled type. The stomach and intestines have well developed glands in the mucous membrane. Masses of pigment accumulate in the mucosa and may be seen breaking through. In general the normal processes have been hastened and exaggerated by excess of thyroid hormone.—T. C. B.

Ligation of the four THYROID arteries in operating for goiter Ueber die Unterbindung der vier Schilddrüsenarterien bei der Kropfoperation). Madlener (M.), Zentralbl. f. Chir. (Leipzig), 1920, **47,** 949-951.

Of technical surgical interest.—J. K.

(THYROID) Adenoma with hyperthyroidism. Mayo (Chas. H.), Ann. Surg. (Phila.), 1920, **72,** 134-140.

A resumé of data presented elsewhere upon this subject by Plummer, Kendall, Boothby and Sandiford of the Mayo Clinic.—J. F.

(THYROID) Basedow's syndrome and tuberculosis (Sindroma de Basedow y tuberculose). Mieres (J. F.), Semana med. (Buenos Aires), 1920, **27,** 507-508.

Tuberculosis is often an etiological factor in Basedow's disease.—B. A. H.

(THYROID) Myxedema after operation for Graves' disease. (Myxödem nach Basedowoperation). Munk, München. med. Wchnschr., 1920, **67,** 945.

A case of Graves' disease in a woman of 19 occurring after the death of her father. The left lobe of the goiter was removed with complete success. Later her mother became insane and the patient nursed her. During this nursing a polyglandular insufficiency with symptoms of myxedema developed.—J. K.

Some structural modifications of the THYROID gland in compensatory hypertrophy (Sur quelques modifications structurales de la glande thyroïde dans l'hyperthrophie compensatrice). Parreira (H.), Compt. rend. Soc. de biol. (Paris), 1920, **83,** 1193-1194.

Of histological interest.—T. C. B.

(THYROID PARATHYROID) Serum changes following thyroparathyroidectomy. Peterson (W.), Jobling (J. W.) & Eggstein (A. A.), J. Exper. M. (N. Y.), 1916, **23,** 499-505.

A study of the serum changes in the tetany produced by thyro-parathyroidectomy. The ferment-antiferment balance, the non-protein nitrogen, the amino nitrogen and the proteose content of the blood were determined in fifteen thyroparathyroidectomized dogs before and at various intervals after the operation. It was found that the protease activity of the serum was increased with a resulting increase in the non-protein nitrogen, the amino-nitrogen and the proteoses. At the same time the lipase titre remained at a very low level in all except one case, in which there was a slight rise. The onset of tetany was found to bear no relation to the ferment-antiferment balance, but the amino nitrogen of the serum was usually increased at the time when tetany was most marked.—I. M.

(THYROID) Goitre, a clinical study of one hundred and thirty-nine cases. Porter (Miles F.), Ann. Surg. (Phila.), 1920, **72,** 129-133.

A summary of the author's experience with goitre since November, 1912.—J. F.

Carcinoma of the THYROID. Rogers (J.), Ann. Surg. (Phila.), 1917, **66,** 222.

This is a note on the author's presentation of cases of cancer of the thyroid gland before the N. Y. Surgical Society. The author said that in his experience carcinoma of this gland has been comparatively rare. In the one dozen cases of which he has records there are two distinct varieties. In one, the new growth develops extensively throughout the greater part of

the gland while in the other it apparently originates and remains confined in some localized portion of the organ. The lymphatics tend to become involved much earlier in the diffuse type.—I. M.

(THYROID) Corneal ulcer of exophthalmic goitre. Rogers (J.), Ann. Surg. (Phila.), 1917, **66**, 222-224.

This is a description of a case of corneal ulcer in exophthalmic goitre. Because of the extreme degree of exophthalmos and edema of the conjunctiva various procedures were attempted to relieve the pressure and to protect the cornea from further erosion. Ligation of the inferior thyroid arteries and section of the lower filaments of the cervical sympathetic and treatment with **adrenal** extract gave little or no relief. The lateral bony walls of the orbit were then partially removed and the eyelids were sutured together after longitudinal incisions were made in each. This last procedure alone gave relief and protection to the cornea.—I. M.

(THYROID) The signs and treatment of thyroidism. Rogers (J.), Med. Rec. (N. Y.), 1917, **92**, 961-962.

This is a short discussion of thyroid disease from the point of view of its physiology, symptomatology and treatment. The author has aimed in all of his operations to protect and save rather than to excise or destroy thyroid tissue, because of his belief that every kind of thyroid disorder is preceded or accompanied by circumstances which involve fatigue. The fatigue state, according to his idea, is followed by a compensatory hypertrophy which later develops into some one of the ordinary diseases of the gland. For treatment, instead of thyroidectomy the author recommends ligation of thyroid arteries for hyperthyroidism and ennucleation of all diseased tissue whether the case be one of hyper- or hypo-thyroidism. Rest and appropriate organotherapy should precede and follow operation in every case.—I. M.

Basal metabolism in THYROID diseases as an aid to diagnosis and treatment with notes on the utility of the modified Tissot apparatus. Rowe (A. H.), Calif. State J. M. (San Fran.), 1920, **18**, 332-334.

From a consideration of 36 cases of actual and supposed hyperthyroidism, the author shows the importance of basal metabolism determinations as a means of differentiating thyroidal disturbances and nervousness. The modified Tissot apparatus is highly recommended.—H. W.

THYROID administration in dementia precox (Proeven met toediening van schildklierstof bij dementia praecox). Schnitzler (J. G.), Psychiat. en neurolog. bladen (Amsterdam), 1916, **20,** 292-302.

Though it is quite probable that there exists a relation between endocrine organs and dementia precox, we know extremely little about this. The author treated some patients with thyroid (as had been recommended in previous literature) without any success.—J. K.

Syphilis as a factor in diseases of the THYROID gland. Simonton (T. G.), Penn. M. J. (Athens), 1917, **21,** 293-296.

Syphilis was found to be the cause of disease of the thyroid gland in five cases observed by the author. All of these cases showed a positive Wassermann reaction and four of them received specific treatment with successful results. Numerous cases studied by others have given similar results. The author concludes, therefore, that a Wassermann test should be made in all cases of tumor or disturbance in function of the thyroid before operation is resorted to.—I. M.

Changes in the THYROID gland following intoxication by toxic protein derivatives. Tatum (A. L.) & Sweet (J. E.), Proc. Path. Soc. (Phila.), 1917, **37,** 22.

The thyroid glands of animals killed by obstruction of the duodenum or by intravenous injection of material found in the intestinal loops were studied histologically The following changes were observed: There was frequently rupture of the alveolar walls with passage of colloidal material into the extra-acinar tissue; desquamation of the epithelium with enlargement of certain cells was common and hyperemia was marked in many instances. The parathyroids and thymus, studied for comparison, appeared quite normal except for a variable degree of hyperemia. A few cases of acute experimental pancreatitis and general peritonitus gave similar results. It is assumed that the poisonous material liberated in these morbid conditions is a product of protein clevage.—I. M.

(THYROID) Surgery of toxic goitre. Terry (W. I.), Ann. Surg. (Phila.), 1920, **72,** 152-154.

The author emphasizes the surgical treatment of toxic adenomata because he finds that they are not curable by medical means. He feels that it is the work of the hygienist to prevent the occurrence of simple goitres. He presents his personal ex-

perience with goitre which is based upon 748 operations. Of these 527 were for toxic goitre in 504 patients. The mortality in this group was 4.3 per cent. The mortality in the group of simple goitre was less than ½ per cent.—J. F.

(THYROID) The heart in goiter (Das Kropfherz). Urban, Wien. klin. Wchnschr., 1920, **33,** 832.

A short note. The operation for goiter is dangerous when there is a typical goitrous heart, which has not been stimulated before the operation.—J. K.

(THYROID) An observed epidemic increase in juvenile goitre in the environs of Budapest (Über eine vorwiegend im Kindesalter beobachtete epidemische Verbreitung des Kropfes in der Hauptstadt Budapest bezw. in deren Umgebung). Vas (J.), Jahrb. f. Kinderh. (Berlin), 1919, **90,** 243-254.

Analysis of the statistics of the Budapest clinics showed a great increase in goitre in children during the war. The incidence the first year of the war was 0.03 per cent, the second year it was 0.08 per cent, the third 0.20 per cent, and the fourth year of the war 0.61 per cent. In July, 1918, the incidence had increased until over 1 per cent of the patients seen in the clinics were affected. Of these cases 70 per cent were females and 85 per cent were over 7 years of age. These cases were studied further from the standpoint of the group and familial incidence of the goitre, and especial attention was paid to underfeeding, occupational factors, and local mechanical causes. Unfortunately this analysis was made largely through the medium of a spot map of the city rather than by a detailed statistical study. However, it led Vas to the belief that there was but a single causal factor involved. He felt that the recent spread of goitre in the city showed an epidemic character similar to an infectious disease especially affecting girls at puberty. This infecting agent perhaps was brought to the capital during the war by the great influx of soldiers, refugees, prisoners, etc., many of whom came from areas of endemic goitre.—C. H. G.

(THYROID) Hyperthyroidism and mental disorders. Walker (W. K.), Penn. M. J. (Athens), 1917, **21,** 300-305; N. York M. J., 1918, **107,** 391-394.

This paper deals with the clinical manifestations of hyperthyroidism which have to do with the central nervous system. The exaggerated symptoms of exophthalmic goitre are compared with those of a violent septic intoxication in which all of the bodily symptoms are overshadowed by mental symp-

toms. From the mental aspect the clinical picture here is characterized by a more or less violent confusion. The association mechanism is prevented from performing its functions properly. Delays and interruptions occur along associative tracts between areas of special sense perception and feelings of strangeness and unreality, bewilderment and oppression with excitement or depression result. Illusions and hallucinations are also comparatively frequent. Milder cases show similar tendencies and in long continued cases various morbid moods appear and suspicional attitudes with mild delusions are observed.

Cases of hyperthyroidism showing a preponderance of mental over physical symptoms are explained by a relative vulnerability of the cortical cells to the toxic products circulating in the blood stream. There is said to be in such cases some destructive alteration of cerebral cortical cells and their intercommunicating fibers.—I. M.

(THYROID) Clinical studies in hyperthyroidism. Watson (L. F.), Med. Rec. (N. Y.), 1917, **91**, 411.

The present paper is the second by the same author on the employment of urea-quinine injections in cases of hyperthyroidism. A few experimental injections of quinine-urea into the thyroid glands of dogs and several hundred injections in 150 human cases of simple and toxic goitre led the author to the following conclusions: 1.—That strong solutions of this substance when injected properly into the thyroid glands are effective in relieving the hyperthyroidism. 2.—Such solutions cause definite destruction of some of the cells and of the colloid present in the alveoli, whereas weak solutions have but little or no effect. 3.—That, while quite harmless in skilled hands, the method offers two dangers when carelessly employed, viz., the possibility of making the injection into the trachea or other neighboring organs and the proneness for myxoedema to follow excessive doses injected directly into the thyroid tissue. 4.—Preliminary injections of isotonic saline solution and distilled water every other day for a short period, before the quinine-urea injection is attempted, raises the patient's threshold to sensory stimuli and so averts an acute attack of hyperthyroidism in the more serious cases.

The method is recommended in special cases of mild toxic goitre and as a preliminary to surgical treatment in cases too severe for immediate operation, but not in cases where large simple goitres are to be removed for cosmetic effects only.

—I. M.

(THYROID) A case of exophthalmic goitre. Welt-Kakels (Sara), Med. Rec. (N. Y.), 1917, **91**, 1161.

A case of a boy 14 years of age who showed striking signs and symptoms of exophthalmic goitre. The case was of special interest because the condition is a rare one in young boys of this age. There was tachycardia, increased blood pressure, exophthalmos, defect in convergence, von Graef's sign and a fine tremor of the fingers. There was a history of emotional shock.—I. M.

(THYROID) The surgery of exophthalmic goitre. Williams (L.), Lancet (Lond.), 1917, **ii**, 950.

In a note to the Editor the author cautions against the statement of Dunhill in a previous issue of The Lancet to the effect that an operation on the thyroid gland is not only justified but obligatory when the symptoms become urgent. The author points out that a large percentage of such cases could be successfully treated by medical measures and that for permanent results in such cases foci of infection such as a diseased appendix, diseased tonsils or gall bladder should be sought and if found removed before thyroidectomy is attempted. When the latter operation is performed without removal of such contributory or underlying factors, the benefits from it can only be temporary. McCarrison is quoted at some length in support of the argument for the more conservative methods of treatment.—I. M.

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With the permission of the editors, certain abstracts have been quoted from "Physiological Abstracts," "Chemical Abstracts" and "Surgery, Gynecology and Obstetrics."